

NUMBER 59 / MARCH 2013

EUROPEAN RESPIRATORY *monograph*

CLINICAL HANDBOOKS FOR THE RESPIRATORY PROFESSIONAL

COPD and Comorbidity

Edited by Klaus F. Rabe,
Jadwiga A. Wedzicha and
Emiel F.M. Wouters



ERS

EUROPEAN
RESPIRATORY
SOCIETY

every breath counts



Published by European Respiratory
Society ©2013
March 2013
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674
Printed by Page Bros Ltd, Norwich, UK

Managing Editor: Rachel White
European Respiratory Society
442 Glossop Road, Sheffield,
S10 2PX, UK
Tel: 44 114 2672860
E-mail: Monograph@ersj.org.uk

All material is copyright to European
Respiratory Society. It may not be
reproduced in any way including
electronic means without the express
permission of the company.

Statements in the volume reflect the
views of the authors, and not necessarily
those of the European Respiratory
Society, editors or publishers.



COPD and Comorbidity

Edited by
Klaus F. Rabe, Jadwiga A. Wedzicha and
Emiel F.M. Wouters

Editor in Chief
Tobias Welte

This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

Contents

Number 59

March 2013

Preface	v
Guest Editors	vii
Introduction	ix
1. Prevalence of COPD and comorbidity <i>Shambhu Aryal, Enrique Diaz-Guzman and David M. Mannino</i>	1
2. COPD: inflammatory mechanisms and systemic consequences <i>Peter J. Barnes</i>	13
3. Assessment of cardiovascular comorbidity <i>John D. MacLay and William MacNee</i>	28
4. Diagnosis and management of heart failure in COPD <i>Frans H. Rutten</i>	50
5. Infection and comorbidity <i>Richa Singh, Alexander J. Mackay and Jadwiga A. Wedzicha</i>	64
6. Malnutrition and obesity in COPD <i>Erica P.A. Rutten, Emiel F.M. Wouters and Frits M.E. Franssen</i>	80
7. Osteoporosis in COPD <i>Elisabeth A.P.M. Romme, Frank W.J.M. Smeenk, Emiel F.M. Wouters and Erica P.A. Rutten</i>	93
8. Gastro-oesophageal reflux disease and COPD <i>Anant R.C. Patel and John R. Hurst</i>	105
9. Metabolic syndrome and diabetes mellitus in COPD <i>Claire E. Wells and Emma H. Baker</i>	117
10. Obstructive sleep apnoea and COPD <i>Walter T. McNicholas and Ruth Lee</i>	135
11. Management of depression and anxiety in COPD <i>Paul A. Cafarella, Tanja W. Effing, Christopher Barton, David Ahmed and Peter Anthony Frith</i>	144
12. Managing skeletal muscle dysfunction in COPD <i>Thierry Troosters, Wim Janssens and Marc Decramer</i>	164

13. Lung cancer in COPD	174
<i>Georgia Hardavella and Stephen Spiro</i>	
14. Pulmonary hypertension in COPD	189
<i>Jordanna Hostler, A. Whitney Brown, John Sherner, Christopher S. King and Steven D. Nathan</i>	
15. COPD and thrombosis	206
<i>Peter K. MacCallum</i>	
16. Comorbidities in current COPD guidelines	217
<i>Per Sigvald Bakke</i>	
CME credit application form	225

Preface



Chronic obstructive pulmonary disease (COPD) is the most common respiratory disease worldwide and has a significant impact on mortality, morbidity and healthcare costs. The incidence of COPD is strongly correlated with age. As such, increasing life expectancy in industrialised societies combined with the fast growth of countries in Asia and Africa mean it is highly likely that COPD will be the most significant chronic disease of all in the future.

For decades, COPD has been viewed as a lung-specific disease. Studies on the effectiveness of therapeutic interventions have focused on lung function and lung function-associated parameters. However, with the increasing number of elderly COPD patients, it has become apparent that many of these patients are also affected by a number of other chronic diseases, such as diabetes, cardiovascular disease, and psychiatric and neurological alterations. COPD is an independent risk factor for the prognosis of these diseases, and, likewise, they influence the prognosis of COPD itself. In recent years, there has been controversial debate about the responsibility of the COPD underlying chronic inflammation in the pathogenesis of other diseases; this has not been definitely confirmed. Factors such as genetic susceptibility and the environment may also explain the frequent co-occurrence of diseases of different organ systems. Regardless of the outcome of this debate, it seems clear that in the future, the prognosis of COPD can no longer be detected using respiratory parameters alone. The influence of therapeutic interventions on the course of comorbidities is not known yet and may be an area of major interest for further study.

COPD and the role of COPD in other diseases clearly demonstrates that respiratory medicine stands at the centre of internal medicine. This leads to several important implications for the future. A department of pneumology has to be established in every general hospital. Diagnostic and therapeutic aspects of the comorbidities also have to be included in pulmonary education and training programmes.

I want to congratulate the Guest Editors Klaus F. Rabe, Jadwiga A. Wedzicha and Emiel F.M. Wouters for the tremendous work they have done in bringing together this excellent, cutting-edge issue of the *European Respiratory Monograph (ERM)*. Readers from many different areas will find this issue useful in their daily work, and it will be of particular interest to both medical doctors and respiratory physicians. I am sure they will find that this issue of the *ERM* provides them with useful guidance on the future of basic and clinical research, and much more.

Guest Editors



Klaus F. Rabe

Klaus F. Rabe is Professor of Pulmonary Medicine at the University of Kiel (Kiel, Germany) and Director of the Department of Pneumology at Lung Clinic Grosshansdorf (Grosshansdorf, Germany). He has been active in various fields of respiratory medicine worldwide, predominantly asthma, COPD and lung cancer.

Professor Rabe took his final exams in medicine at the University of Hamburg (Hamburg, Germany) in 1983 and his clinical education began at Marienkrankenhaus Hamburg (1983–1987) where he then spent time working at Universitätskrankenhaus Eppendorf (University of Hamburg) within the intensive care and endoscopic units. In 1988, Professor Rabe worked in the pulmonary division of Krankenhaus Grosshansdorf, the Centre for Pneumology and Thoracic Surgery (Grosshansdorf), and then in 1989, he worked in clinical research in the Department of Thoracic Medicine of the National Heart and Lung Institute (London, UK). In 1998, Professor Rabe was nominated Professor of Medicine at the University of Leiden (Leiden, the Netherlands) where he was also appointed as the Chairman of Pulmonology, and later, in 2007, as the Chairman of Medicine. In 2010, he moved back to Germany into his current position.

Professor Rabe has served on various editorial boards, was the first European Associate Editor of the *American Journal of Respiratory and Critical Care Medicine* and was co-Chief Editor of the *European Respiratory Journal*. His current scientific interests are related to large clinical trials in COPD and asthma, the mechanisms of airway inflammation, and the endoscopic staging of lung cancer. Professor Rabe has served on the boards of the Global Initiative for Asthma (GINA) and the Global Initiative of Chronic Obstructive Lung Disease (GOLD), and is a member of the German and Dutch Chest Societies, the British Pharmacological Society, and the American Thoracic Society (ATS). He is the immediate Past-President of the European Respiratory Society (ERS).



Jadwiga A. Wedzicha

Jadwiga A. Wedzicha is Professor of Respiratory Medicine at the UCL Medical School and the Royal Free Hospital (both London, UK). She qualified from Somerville College (Oxford University, Oxford, UK) and St Bartholomew's Hospital Medical College (University of London, London).

Professor Wedzicha has a major interest in the causes, mechanisms, impact and prevention of COPD exacerbations and in the role of bacterial and viral infection in COPD exacerbation. She directs an active research group into COPD exacerbations and has published extensively on this topic.

Professor Wedzicha chairs the English Department of Health Home Oxygen Clinical User Group, and was a member of the Guideline Development Group for the revision of the NICE COPD Guidelines. She is also a member of the Programme Board for the English COPD National Clinical Strategy.

Professor Wedzicha was Editor-in-Chief of *Thorax* from 2002 to 2010, and is a member of the BioMed Central and the *American Journal of Respiratory and Critical Care Medicine* advisory boards. She is also a member of the editorial boards of a number of international journals. Until 2012, she was Guidelines Director for the European Respiratory Society (ERS) and is currently the Publications Committee Chair of ERS Publications.



Emiel F.M. Wouters

Professor Emiel F.M. Wouters studied medicine at the Catholic University of Leuven (Leuven, Belgium), where he graduated in 1978. He was trained in internal medicine at the Annadal Hospital Maastricht (Maastricht, the Netherlands) and the University Hospital Leuven (Leuven). In 1981, he started his residency at the Department of Pulmonology of the University Hospital Maastricht (Maastricht) and was registered as a pulmonologist in July 1984. He received his PhD for his thesis, entitled “Bronchial response in COPD measured by forced oscillation technique”, at the same university in 1987. After his appointment to Associate Professor of Pulmonology in 1988, he became Full Professor and Chairman of the Department of Respiratory Medicine of the University Hospital Maastricht in 1992 and Chairman of the Medical Board of the Asthma Centre Hornerheide (Horn, the Netherlands). He is currently involved in research into inflammation and multi-component pathology of COPD.

Professor Wouters has acted as Chair of the Scientific Board of the Dutch Asthma Foundation, as well as Chair of the Rehabilitation and Chronic Care Group of the European Respiratory Society (ERS). He was Chief Editor of the *European Respiratory Monograph (ERM)* until 2005. Professor Wouters is the Director of the Centre for Chronic Diseases of the Maastricht University Medical Centre (Maastricht, the Netherlands), the Chief Executive Officer of the Centre for Integrated Rehabilitation of Chronic Organ Failure (CIRO Horn) and the research leader of the COPD Centre of Excellence of the NUTRIM (Nutrition, Toxicology and Metabolism) Research School (Maastricht University Medical Centre). He is also visiting professor at the University of Vermont (Burlington, VT, USA).

Professor Wouters fulfils different memberships of the scientific boards and task forces of respiratory medicine, and has published as (co)author of more than 500 papers in scientific journals, largely related to COPD.

Introduction

Klaus F. Rabe^{*#}, Jadwiga A. Wedzicha[¶] and Emiel F.M. Wouters⁺

^{*}Dept of Internal Medicine, Christian Albrechts University Kiel, Kiel. [#]Lung Clinic Grosshansdorf, Grosshansdorf, Germany. [¶]Centre for Respiratory Medicine, University College London, London, UK. ⁺Maastricht University Medical Center, Maastricht University, Maastricht, the Netherlands.

Correspondence: J.A. Wedzicha, Centre for Respiratory Medicine, University College London, Rowland Hill Street, London, NW3 2PF, UK. Email: w.wedzicha@ucl.ac.uk

COPD is a common and progressive chronic inflammatory condition that is responsible for a large amount of morbidity and mortality globally, and affects millions of people worldwide. It is now recognised that COPD is a heterogeneous disease and that the severity of the airflow obstruction, as determined by the forced expiratory volume in 1 second (FEV₁), is not the best determinant of the severity of COPD and its impacts. Thus, severity of this disease is now determined by the combination of symptoms, future risk that is mainly related to exacerbation frequency, and FEV₁ stage.

COPD is not only associated with airway inflammation but also with considerable systemic inflammation, though the precise relationship between the airway and systemic inflammatory processes in COPD remains to be elucidated. It has been proposed that this systemic inflammation is responsible for the considerable comorbidity that is seen in COPD. Thus, COPD is a disease that reaches far outside the lung, and comorbidity is found in all stages of COPD even in patients with mild and moderate COPD by FEV₁ stage. Cigarette smoking is the main risk factor for COPD and it is also a risk factor for other major diseases, such as cancer and cardiovascular disease, which are also more common with increasing age. These comorbidities will have an influence on the severity of COPD, and need to be addressed in severity and impact scores for COPD. Management of comorbidities will also have an effect on outcome in COPD; there is, for example, emerging data that COPD patients with cardiovascular risk who are treated with beta blockers have a better outcome, particularly when admitted to hospital with COPD exacerbations. Similarly, bronchodilator and anti-inflammatory therapy in COPD may impact on the degree of comorbidity, although historically, COPD patients with comorbidities have been excluded from clinical trials.

This issue of *European Respiratory Monograph (ERM)* aims to address the inter-relationships of COPD and comorbidity, a very wide and diverse topic, as can be seen from the contents list. There has been considerable recent emphasis on the study of comorbidity in COPD and a number of new studies have been published. Thus, the chapters are up to date, well referenced and written by a team of international experts with a clinical focus.

The *ERM* starts with a description of the epidemiology of comorbidity as applied to COPD, and this is followed by a description of inflammatory mechanisms of COPD and how these relate to comorbidity. The chapters that follow discuss cardiovascular disease in COPD; there has been much interest in cardiovascular comorbidity as it accounts for a considerable amount of mortality in COPD. However, cardiovascular disease is often unrecognised in COPD and it is important to understand its impact both during exacerbations and when patients are stable. Heart failure is common in an ageing population and thus frequently coexists in COPD with overlap of symptoms. Pulmonary hypertension affects the prognosis of COPD but may often be undetected. Airway infection contributes to the mechanisms of both stable COPD and exacerbations, and it is known that airway infection may be associated with increased cardiovascular events and haematological abnormalities. Pneumonia is an important comorbidity in COPD, with recent data

suggesting that it may be precipitated by inhaled corticosteroid therapy. COPD patients are current or previous smokers and are at increased risk of lung cancer.

Metabolic conditions are also important comorbidities, and this issue of the *ERM* includes chapters that address obesity in malnutrition in COPD, obstructive sleep apnoea, and osteoporosis, which is one of the most common comorbidities in COPD and is potentiated by the effect of inactivity and corticosteroids. Diabetes affects both stable and exacerbated COPD, and improved diabetic control may benefit exacerbation outcome. Associations have been shown between exacerbation frequency and gastro-oesophageal reflux that will be discussed in this issue of the *ERM*, though the actual mechanisms of reflux in COPD are not clear and may relate to the mechanical effects of hyperinflation. Inactivity is related to prognosis in COPD and skeletal muscle dysfunction needs to be assessed and targeted. Psychological disease (anxiety and depression in particular) is often present in COPD and must be targeted; it is particularly common in patients who have a higher exacerbation risk.

Thus, clinical programmes for the management of COPD patients must not only treat airways disease but should also assess and manage the associated comorbidities. This will make COPD management a much more complex, long-term process in the future, requiring multi-disciplinary teams with relevant specialist interests. It is essential that clinical trials include and, wherever possible, specifically target patients with comorbidities, as respiratory therapies may improve comorbidities. At the same time, any adverse effect of therapies on comorbidities in an increasingly ageing population must be recognised early and where patients require multiple pharmacological approaches, optimal adherence to therapy must be ensured. Current therapies for COPD are actually relatively limited and thus it is possible that therapies targeting comorbidities may have a significant impact on health status and mortality in COPD. Further research and evidence is required to inform future guidelines on the relationship of complex comorbidity in COPD.

We hope that you will find this issue of the *ERM* a useful resource that aids understanding of the role of comorbidity in COPD and the way in which comorbidity potentially influences disease management. This book will be of benefit to a wide number of healthcare professionals, including clinicians, nurses and allied healthcare professionals, but it will also be of interest to those specialising in the management of comorbidities, such as cardiologists and gastroenterologists. The chapters are up to date and well referenced, and will stimulate novel ideas for research and inspire healthcare professionals in training. We are very grateful to all the authors who have contributed excellent chapters on such an important and yet relatively poorly understood and researched topic.

Chapter 1

Prevalence of COPD and comorbidity



Shambhu Aryal*, Enrique Diaz-Guzman* and David M. Mannino*[#]

SUMMARY: COPD, once thought only to be a disease of the lungs, is now established as a common complex multisystem disease with multiple comorbidities that contribute to symptoms, exacerbations, hospital admissions and mortality. The most notable of these comorbidities include cardiac and cerebrovascular disease, diabetes, hypertension, asthma, pneumonia and depression. Estimation of the prevalence of COPD, as well as its comorbidities, is difficult because of the variability in definitions and methods used. However, recent large epidemiological studies have helped us to understand better the prevalence and effects of COPD comorbidities. The pathogenesis behind many of these comorbidities remains a focus of active investigation. Successful management of COPD comorbidities is central to improving overall outcomes in COPD.

KEYWORDS: Comorbidity, COPD, human pathology, outcomes, prevalence

*Division of Pulmonary and Critical Care Medicine, University of Kentucky, and

[#]Dept of Preventive Medicine and Environmental Health, University of Kentucky, Lexington, KY, USA.

Correspondence: D.M. Mannino, Dept of Preventive Medicine and Environmental Health, University of Kentucky, 111 Washington Ave, Lexington, KY 40536, USA.
Email: dmmann2@email.uky.edu

Eur Respir Monogr 2013; 59: 1–12.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011012
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

COPD is a heterogeneous disease that is characterised by progressive and not fully reversible airflow obstruction, and is associated with multiple comorbidities and systemic consequences. It is a common condition, especially in older adults, and carries a significant morbidity and mortality, as well as a tremendous economic burden on individuals, families and the society. Epidemiological studies over the last several decades have provided insight into the aetiology, prevalence and pathogenesis of COPD. This chapter will summarise what is known about the prevalence of COPD and its comorbidities.

Definition of COPD

The definition of COPD has evolved over the last two decades. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined COPD as “a common and preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.” [1]. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have largely adopted the GOLD definition in their latest guidelines stressing the

preventable and treatable nature of the syndrome, and incomplete reversibility of airflow limitation, as well as the importance of its comorbidities and systemic consequences [2].

The criteria used for defining airflow limitation and reversibility have also evolved over the years. Currently, a forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio of <70% continues to be accepted as the definition of airflow limitation [1]. Although this “fixed” ratio is simple and easily remembered, it has been criticised for its potential to misclassify patients, underestimate COPD in younger populations and overestimate it in older populations [3]. Consequently, the ERS Task Force on recommendations for epidemiological studies of COPD recommends using a lower limit of normal at 5% to define COPD [4].

Disease severity in COPD has typically been determined using the degree of lung function impairment. The most current GOLD and ATS/ERS criteria classify COPD into the following four stages. Stage I: FEV₁ ≥ 80% predicted; stage II: FEV₁ 50 to <80% pred; stage III: FEV₁ 30 to <50% pred; and stage IV: FEV₁ <30% pred [1, 2]. However, many recent studies suggest that several other factors, such as fat-free body mass, functional status, exercise capability, arterial blood gases and the presence of comorbid diseases, should be taken into account to assess severity [4]. The most recent GOLD stratification of COPD uses a combination of symptomatic assessment with the patient’s spirometric classification and/or risk of exacerbations to classify patients to either category A (low risk, fewer symptoms), B (low risk, more symptoms), C (high risk, fewer symptoms) or D (high risk, more symptoms) [1].

Prevalence of COPD

Estimation of the prevalence of COPD and its comorbidities remains difficult due to variability in definitions over the years and methods used in different studies. The best means of determining the burden of COPD in the population is by measurement of lung function, which is least likely to be affected by any type of diagnostic or reporting bias; moreover, lung function is a reasonable predictor of mortality and functional limitations [5]. However, it must be remembered that the quality of spirometry is extremely important and if poor, may lead to over-diagnosis of cases.

Based on the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of COPD in the USA is about 13.5%, most of this being mild to moderate [6]. In Europe, the prevalence of COPD has been estimated to be anywhere between 2% (the Netherlands) to more than 10% (Austria and Germany) [7]. In South America, the PLATINO (Proyecto Latino-Americano de Investigación en Obstrucción Pulmonar) study estimated a prevalence of COPD in those older than 40 years of age to be estimated at between 7.8% and 20% [8].

In 2006, a meta-analysis of studies of the general population published between 1990 and 2004 around the world estimated the prevalence of COPD to be 7.6% (95% CI 6–9.2%); the pooled prevalence from 26 spirometric estimates was 8.9%. The analysis also revealed geographical disparities and differing methodologies [9]. In subsequent years, the Burden of Obstructive Lung Disease (BOLD) study provided a unique opportunity to estimate the prevalence of COPD in population based-samples in adults aged more than 40 years of age, in both developed countries and developing countries, using a standardised protocol for questionnaires and lung function testing. The prevalence of patients at stage II or more was estimated at 10.1%; 11.8% for males and 8.5% for females, with heterogeneity across centres and sex. The high prevalence of COPD in females and in subjects who had never smoked also suggested that genetic predisposition and exposures other than smoking could be important [10]. Figure 1 summarises the estimated prevalence of COPD in different regions of the world based on the two large studies discussed previously [6].

Morbidity, mortality and the economic burden

COPD is currently the fourth leading cause of death worldwide and is projected to be the third leading cause of death by 2020 [11]. A pooled analysis of multiple studies on COPD between 2000

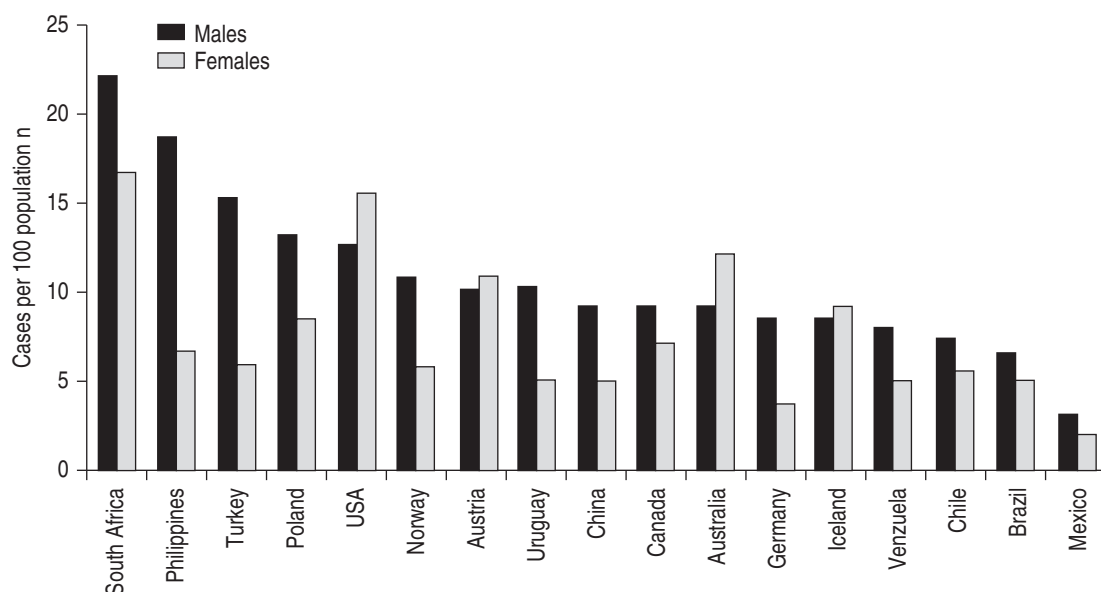


Figure 1. Estimated prevalence of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II or higher COPD. Data are taken from the PLATINO (Proyecto Latino-Americano de Investigación en Obstrucción Pulmonar) study and the Burden of Obstructive Lung Disease (BOLD) project. Estimates are for small regions of the countries listed and do not necessarily represent national prevalence estimates. Reproduced from [6] with permission from the publisher.

to 2010 from PubMed and Embase databases showed that the global 1-year mortality varied from 4% in people aged 45 years and older to as high as 28% in people aged 65 years and older [12]. The overall mortality rate varied from 3 to 111 per 100,000 people, and was greater in males. Among smoking-related deaths, 20% in females and 50% in males were attributable to COPD.

The morbidity and economic costs associated with COPD are very high and generally unrecognised. The World Health Organization (WHO) predicts that by 2020 COPD will rank fifth as a worldwide burden of disease and chronic disability [13]. A study from the USA found that even after adjusting for various confounders, employed adults with COPD reported significantly lower quality of life and work productivity, and increased healthcare resource utilisation than employed adults without COPD [14]. The economic burden from COPD has been increasing for the past several years [15]. In the USA, the annual cost of COPD overall is estimated to be in excess of \$40 billion [16]. Similarly, in a European study, the cost of COPD was €478 and €284 per patient per year in Iceland and Norway, respectively; the estimated cumulative costs of COPD for the population aged ≥ 40 years was €130 million and €1,539 million for the following 10 years in Iceland and Norway, respectively [17]. Although these figures on mortality, morbidity and economic cost are alarming, they may only represent the “tip of the iceberg”, as COPD rarely occurs in isolation but is often part of a more complex multisystem syndrome with a large number of associated comorbidities [16].

Comorbidities of COPD

In COPD, comorbid conditions, or comorbidities, may be defined as other serious diseases and chronic medical conditions that affect persons who have COPD [17]. There are several important comorbidities of COPD [18]; these have been aptly represented in a “comorbidome” (fig. 2) by Divo *et al.* [19]. Comorbidities differ from systemic consequences of COPD; the latter are thought to be direct consequences of the disease. However, both influence the course of the disease [20]. For example, ischaemic heart disease is a common comorbidity in COPD while cor pulmonale is a known systemic consequence. Several factors add to the complexity of studying comorbidities and

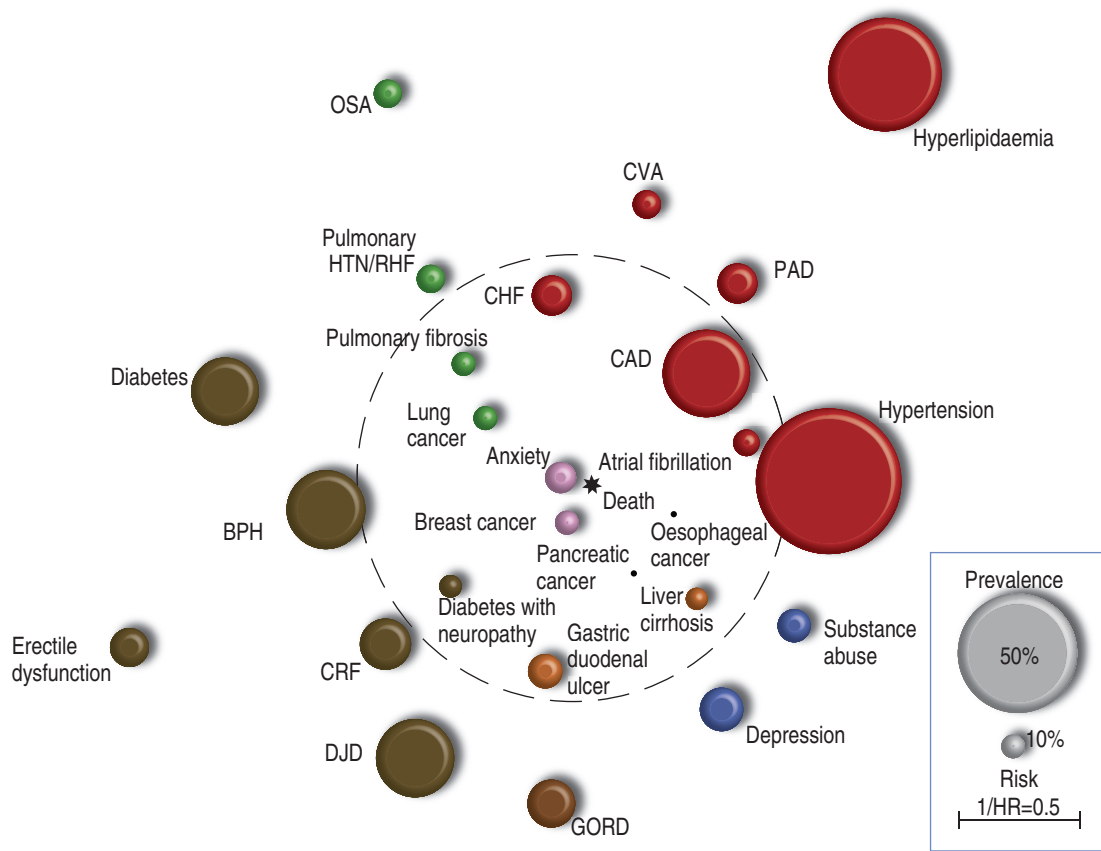


Figure 2. The “comorbidome” is a graphical expression of comorbidities with >10% prevalence in the entire cohort, and those comorbidities with the strongest association with mortality (hazard ratio (HR) >1, 95% CI >1; $p \leq 0.05$). The area of the circle relates to the prevalence of the disease. The proximity to the centre (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the HR (1/HR). All bubbles associated with a statistically significant increase in mortality are fully inside the dotted orbit (1/HR <1). The colours of the bubbles represent organ systems or disease clusters. Red: cardiovascular; pink: female-specific comorbidities; green: pulmonary; blue: psychiatric; brown and orange: others. OSA: obstructive sleep apnoea; CVA: cerebrovascular accident; HTN: hypertension; RHF: right heart failure; CHF: congestive heart failure; PAD: peripheral artery disease; CAD: coronary artery disease; BPH: benign prostatic hypertrophy; CRF: chronic renal failure; DJD: degenerative joint disease; GORD: gastro-oesophageal reflux disease. Reproduced from [19] with permission from the publisher.

outcomes in patients with COPD. These include smoking history, ageing, polypharmacy, medication interactions, coding inaccuracy of diagnoses and lack of specific case definitions for some of the comorbidities [21]. Comorbidities play an important role in COPD for several reasons. First, they may share similar pathophysiological mechanisms with COPD. Secondly, they have a significant impact on health status, healthcare utilisation and all-cause hospital admissions in COPD patients. Thirdly, mortality due to associated comorbidities, such as cardiovascular disease or malignancy, can occur earlier than respiratory causes. Finally, understanding clusters of comorbidities may be useful to better phenotype COPD with diagnostic, therapeutic and prognostic implications.

Classification of comorbidities

Traditionally, the various comorbidities of COPD have been classified by authors into different groups using the historic clinicopathological approach for human diseases (table 1). Recently, LOSCALZO [22] proposed a novel, holistic method for classifying human diseases based on common

Table 1. Classification of comorbidities of COPD

Based on common human pathological mechanisms

1. Inflammation/immune response: asthma, pneumonia, idiopathic pulmonary fibrosis, ischaemic heart disease, osteoporosis, skeletal muscle dysfunction and metabolic syndrome
2. Apoptosis/necrosis/degeneration: cardiovascular diseases, malignancies, metabolic syndrome, osteoporosis, skeletal muscle dysfunction and gastro-oesophageal reflux disease
3. Trauma and repair/cell proliferation and neoplasia/fibrosis: malignancies and musculoskeletal dysfunction
4. Thrombosis/haemorrhage: pulmonary embolism, ischaemic heart disease and cerebrovascular diseases
5. Unknown: depression and chronic renal failure

Based on clinicopathological approach

1. Respiratory: asthma, pneumonia, pulmonary embolism, pulmonary hypertension, idiopathic pulmonary fibrosis, obstructive sleep apnoea and lung cancer
2. Cardiovascular: ischaemic heart disease, arrhythmias, congestive cardiac failure, strokes and hypertension
3. Metabolic: metabolic syndrome, diabetes, hypertension, dyslipidaemia, osteoporosis and skeletal muscle dysfunction
4. Malignant: lung cancer, oesophageal cancer and breast cancer
5. Psychiatric: depression, anxiety and insomnia
6. Miscellaneous: renal failure, gastro-oesophageal reflux disease/peptic ulcer disease and erectile dysfunction

human pathological mechanisms. This approach could be used to classify the comorbidities of COPD with a better understanding of their pathobiology and, consequently, treatment and outcomes (table 1).The pathogenesis of COPD is beyond the scope of this chapter; therefore, readers are directed to chapter 2 [23]. The next section will discuss the prevalence of COPD comorbidities based on the traditional clinicopathological classification.

Prevalence of comorbidities in COPD

The prevalence of COPD comorbidities varies significantly between studies based on the populations, definitions and methods used. Table 2 is a summary of some of the studies that have investigated the prevalence of comorbidities of COPD over the last decade. It is noteworthy that the population source and mean age of the population varies within the studies. Moreover, the definition of individual comorbidity was not uniform across studies. In most cases, the conditions are self-reported and seldom graded. Also, the variation in inclusion and exclusion criteria of the different studies also leads to an inaccurate estimation of these studies. In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study for example, subjects with inflammatory diseases were excluded which may have affected the observed prevalence of comorbidities [33].

There seems to be a paucity of literature on the difference of prevalence of COPD comorbidities across the sexes. However, available data suggest that they tend to follow the same distribution as in the general population. For example, ischaemic heart disease, diabetes and hypertension are more common in males, and osteoporosis and depression are more common in females [26, 28, 30, 34].

Respiratory

Several respiratory conditions have been found to coexist and complicate the course of patients with COPD. Notable among those are asthma, pneumonia, pulmonary embolism, pulmonary hypertension, obstructive sleep apnoea and lung cancer.

Traditionally, many studies have tried to segregate people with obstructive airway diseases into those with asthma or COPD. Nevertheless, evidence suggests that asthma tends to coexist in a proportion of patients with COPD, especially the elderly [35], in whom the prevalence of coexistence can be as high as 40%.

Pneumonia is viewed by some as a part of the spectrum of COPD exacerbations; however, there are important differences between the two. Patients with COPD and pneumonia have more abrupt onset of symptoms, more severe illness, longer length of stay, and higher rates of intensive care

Table 2. Summary of studies investigating prevalence of comorbidities of COPD

Study	Population source	Age years	Comorbidities									
			Respiratory	Cardiac	DM	HTN	Lipids	Skeletal	Malignant	Psychiatric	GI	Renal
MAPEL [24]	In-patient and outpatient	67.5		65	12	45		22	18	17	32	1.5
VAN MANEN [25]	General practice	66 ± 11		13	5	23		36	6	9	15	6
SORIANO [26]	General practice	65 ± 15	28	22				28	4	10	26	5
SIDNEY [27]	In-patient	50	40 [#]	18	2	18		9				0.6
WALSH	General practice		22 [†]	50	16	52	51	42	17	35	62	
ANECCCHINO [28]	HSDB	70		64	12					8		
MANNINO [29]	HSDB	57		15	13	40						
CAZZOLA [30]	HSDB	65		60	19			15	2	32		
AGUSTI [31]	General practice	63 ± 7		26	10			14		17	27	
FEARY [32]	HSDB	70		38	12							

Data are presented as mean, mean ± sd or % of the study population. DM: diabetes mellitus; HTN: hypertension; GI: gastrointestinal; HSDB: health service database. [#]: prevalence of asthma in this study; [†]: prevalence of obstructive sleep apnoea in this study.

unit (ICU) admission and death [36]. Also, some COPD therapies, like salmeterol and fluticasone, have been shown to increase the incidence of pneumonia but decrease the incidence of exacerbations [37]. In a study that included 707 patients presenting with community-acquired pneumonia, 19% had COPD while in 10% of the cases, pneumonia led to a new diagnosis of COPD [38].

Pulmonary embolism is thought to be a common comorbid condition in patients with COPD, although the data are somewhat controversial. In a study of 211 consecutive patients admitted for severe exacerbation of COPD of unknown origin and undergoing spiral computed tomography (CT) or ultrasonography, researchers found that 25% had pulmonary embolism [39]. In contrast, a more recent study reported a much lower incidence of pulmonary embolism in 123 consecutive patients admitted for acute exacerbation of COPD: 6.2% among patients with a high clinical suspicion of pulmonary embolism and 1.3% among patients with a low clinical suspicion of pulmonary embolism [40].

Pulmonary hypertension is a known systemic consequence of COPD but some people with COPD have “out-of-proportion” pulmonary hypertension, defined as a mean pulmonary artery pressure >35–40 mmHg and a relatively preserved lung function, which cannot explain prominent dyspnoea and fatigue. The prevalence of this out-of-proportion pulmonary hypertension is believed to be close to that of idiopathic pulmonary hypertension [41].

Idiopathic pulmonary fibrosis (IPF) is increasingly recognised to coexist with COPD. A recent study found that the prevalence of IPF in people with COPD is as high as 6%. Moreover, it was an independent predictor of mortality [19].

The prevalence of obstructive sleep apnoea syndrome in people with COPD is the same as in the general population, at around 5%; however, patients with concomitant COPD and obstructive sleep apnoea have higher pulmonary artery pressures, increased incidence of right heart failure, and more hypoxia and hypercapnia for a similar level of lung function [42]. These patients also have an increased risk of hospital admission for COPD exacerbation and higher mortality than COPD patients without obstructive sleep apnoea and this risk decreases with use of continuous positive airway pressure [34].

Cardiovascular and cerebrovascular

A wide variety of cardiovascular conditions afflict people with COPD, including coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular diseases, arrhythmias and hypertension. Cardiovascular disease is the leading cause of death in patients with mild-to-moderate COPD. In a pooled analysis of two large population-based epidemiological studies by MANNINO *et al.* [29], the prevalence of cardiovascular disease (defined as ischaemic heart disease, heart failure, stroke and/or transient ischaemic attack) in COPD patients was found to be 20–22% compared with 9% in subjects without COPD. These increases were particularly amplified in COPD patients with GOLD stage III and IV disease rather than those with mild-to-moderate COPD (fig. 3) [29]. Similarly, in a recent study from Germany, GOLD categories B and D were characterised by a higher degree of dyspnoea than groups A and C, and had a five to eight times higher mortality from cardiovascular disease (and cancer) [43].

The main cardiovascular comorbidity in COPD is ischaemic heart disease. Multiple studies have demonstrated that the prevalence and odds of development of ischaemic heart disease in people with COPD are considerably higher compared to controls even when adjusted for known cardiovascular risk factors [26, 33, 44]. In the ECLIPSE study, “heart trouble” was reported in 26% of 2,164 COPD patients compared with 11% of 337 smoking controls ($p<0.001$), with a myocardial infarction reported in 9% *versus* 3% ($p<0.001$) [31].

Heart failure is a complex clinical syndrome with many features in common with COPD. The overall prevalence of heart failure in COPD in the ECLIPSE study was 7% [31] and increased with the severity of airflow limitation. The prevalence of cardiac arrhythmia in COPD is estimated to be approximately 12% [26], with atrial fibrillation being the most common type.

Cerebrovascular diseases are also quite common in people with COPD. FEARY *et al.* [32] reported the prevalence of stroke as 9.9% in those with COPD compared with a background prevalence of 3.2% in the rest of the population. In the longitudinal part of the study, COPD was associated with a 2.8-fold increase in the incidence of acute stroke. Despite the reported prevalence and relative importance of stroke, there is limited data on its symptomatic and functional impact on COPD.

Metabolic

Metabolic syndrome is a complex disorder recognised clinically by the findings of abdominal obesity, elevated triglycerides, atherogenic dyslipidaemia, elevated blood pressure, and high blood glucose and/or insulin resistance. Patients with COPD often have one or more component of the metabolic syndrome and osteoporosis which are thought to be independent of treatment with steroids and/or decreased physical activity [45].

Hypertension is consistently one of the most prevalent comorbid diagnoses in COPD. In the pooled analysis of two large population-based cohorts by MANNINO *et al.* [29], the prevalence of hypertension was 34% in normal subjects, increasing to 40% in GOLD stage I patients, 44% in GOLD stage II

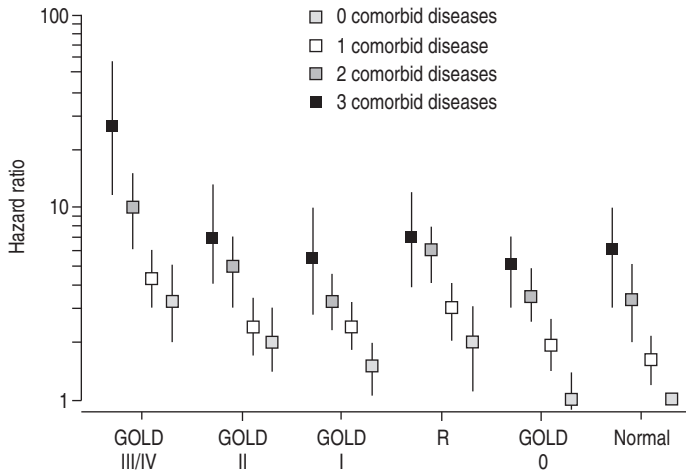


Figure 3. Prediction of death within 5 years by modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories and the presence of none, one, two or three comorbid diseases (diabetes, hypertension or cardiovascular disease). The reference group (normal) was subjects with normal lung function for each comorbid disease. Models were adjusted for age, sex, race, smoking status, education level and body mass index. R: restrictive lung disease. Reproduced from [29] with permission from the publisher.

and 51% in GOLD stage III and IV patients. Hypertension is a key risk factor for atherosclerotic diseases, haemorrhagic stroke and cardiac arrhythmias; therefore, its sequelae may have a profound impact on COPD patients.

Type II diabetes is more prevalent in moderate-to-very severe COPD than in the general population, with an overall prevalence of 12.7% [29]. Although some non-diabetic patients have hyperglycaemia induced by systemic corticosteroids, many more have truly overt diabetes.

Studies on dyslipidaemia in COPD are limited and have relied on questionnaires or diagnostic codes to determine frequency; the prevalence based on these studies is between 9% and 51% (table 2). Despite that, there is a growing body of evidence that statin therapy is beneficial in COPD patients, beyond its important effects on cardiovascular risk reduction; this may be related to the anti-inflammatory properties of statins [46].

Osteoporosis and osteopenia are more prevalent in COPD than control subjects and are related to disease severity, CT-quantified emphysema score, arterial stiffness, systemic inflammatory markers, body mass index (BMI) and physical activity [47]. Systemic steroids remain the most common cause of drug-related osteoporosis; the role of inhaled corticosteroids in the development of osteoporosis is still a matter of controversy.

Skeletal muscle dysfunction and cachexia is also quite common in COPD for many reasons including inactivity, use of systemic glucocorticoids, malnutrition, and possibly systemic inflammation and oxidative stress. One study reported that up to 45% of COPD patients who qualified for pulmonary rehabilitation were underweight and had muscle wasting [48].

Malignancy

Lung cancer is an important cause of mortality in COPD. Depending on studies, lung cancer has been found to be the cause of death in 7–38% of patients with COPD [21]. The risk of developing lung cancer has been shown to be proportional to the severity of airway obstruction; this correlation is stronger than with the degree of smoking. Compared to smokers with normal lung function, hazard ratios (HRs) for developing lung cancer for patients with mild-to-moderate and severe COPD ranged between 1.4 and 2.7, and 2.8 and 4.4, respectively [49]. The risk of lung cancer was 3.5-fold higher for females than males at similar levels of FEV₁ [50].

COPD patients are also at increased risk of extrapulmonary malignancies, although there is limited research in this area. Intuitively, the prevalence of smoking-related cancers, such as oesophageal, pancreatic and bladder, should be significant in people with COPD. Extrapulmonary cancers also seem to be associated with mortality (fig. 2). In one study, COPD was also associated with an increased risk of death from extrapulmonary cancer, with a HR of 1.43; the relationship was significant for moderate COPD (HR 1.70), but not for severe COPD, nor for patients with mild COPD [51].

Psychiatric

Depression is a common comorbidity of most symptomatic chronic diseases that have great implications; its prevalence may be higher in COPD than other chronic diseases [52]. Data from the ECLIPSE study showed around 25% of COPD patients had depression, defined as the score on a validated questionnaire, compared with 12% of control subjects [53]. It is widely acknowledged that depression is under-recognised in COPD and screening questionnaires may be a useful adjunct to a clinical diagnosis, upon which management should be based. Pulmonary rehabilitation, pharmacological antidepressants and psychotherapeutic strategies may all be beneficial, but more work is required to optimise the management pathway of these individuals.

Anxiety and insomnia are also thought to be relatively more prevalent in COPD patients but no consistent data in the available literature currently exist. A recent study found the prevalence of anxiety to be as high as 20% [19].

Miscellaneous

Chronic renal failure (CRF) is another comorbidity of COPD that requires more research. In a cohort of 365 patients, the prevalence of concealed (with normal glomerular filtration rate) and overt CRF in patients with COPD was 20.8% and 22.2%, respectively, compared to 10.0% and 13.4%, respectively, in controls [54]. Diabetes, hypo-albuminaemia and musculoskeletal diseases were significant correlates of concealed CRF while BMI and diabetes were significantly associated with overt CRF [47].

Symptomatic gastro-oesophageal reflux disease (GORD) and peptic ulcer disease occur in up to 30–60% of COPD patients [55]; many more asymptomatic GORD are detected by oesophageal manometry. There are reasons why reflux may be more prevalent in COPD, including a low lying diaphragm from hyperinflation, coughing and increased use of abdominal muscles for ventilation [47]. Data from the ECLIPSE study identified a history of heartburn or reflux as an independent predictor of frequent COPD exacerbations [56].

COPD comorbidities and outcomes

The presence of both COPD and other comorbidities is associated with poor health outcomes. COPD patients are more likely to die from a comorbid disease than COPD itself. The data from the TORCH (Towards a Revolution in COPD Health) study demonstrated this nicely (table 3) [57]. Of the 911 deaths in patients with well-characterised COPD, only 40% of the deaths were definitely or probably related to COPD. The remainder were mostly unrelated to COPD (50%) or of unknown cause (9%).

Comorbidities are important to many of the hospitalisations in COPD patients. In the Lung Health Study, 12.8% of the 5,887 smokers were hospitalised, with 42% of the hospitalisations secondary to cardiovascular events or pulmonary complications [58]. In a study of more than 45,000 patients with COPD, heart failure was the leading cause of hospitalisation, followed by myocardial infarction and stroke [27]. KINNUNEN *et al.* [59] found that comorbidities had an impact on the duration of COPD hospitalisations, and reported a mean length of stay of 7.7 days without any comorbidity compared with 10.5 days if a concurrent disease was present.

Comorbidities also influence outcomes of COPD exacerbations. A study evaluated hospital mortality, length of stay, and death and readmission at 90 days after index admission for a COPD exacerbation [60]. Prevalence of comorbidities was associated with worse outcomes for all four measures. Hospital mortality risk was increased with cor pulmonale, left ventricular failure, neurological conditions and non-respiratory malignancies, whilst 90-day mortality was also increased by lung cancer and arrhythmias. Ischaemic and other heart diseases were important factors in readmission.

Finally, the economic burden of comorbidities in COPD is significant. An analysis of the Maryland Medicaid database, for example, showed that compared with the controls, Medicaid COPD patients had higher comorbidity burden. These COPD patients, on average, had 24% more medical claims (81.4 *versus* 65.4, $p<0.001$) and were 33% more expensive than controls (\$7,603 *versus* \$5,732, $p<0.001$) [61].

Conclusion

COPD is a complex and a heterogeneous disease. The vast majority of patients have comorbidities.

Table 3. Cause-specific mortality in 911 COPD patients in the TORCH study

System	Subjects %
Cardiovascular	26
Congestive heart failure	3
Myocardial infarction	3
Stroke	4
Sudden death	16
Respiratory	35
COPD	27
Pneumonia	8
Other	<1
Cancer	21
Lung	14
Other	7
Other cause	10
Unknown cause	8

TORCH: Towards a Revolution in COPD Health. Reproduced from [57] with permission from the publisher.

Pulmonary and extrapulmonary comorbidities share pathophysiological links and have a profound impact on morbidity and mortality, as well as economic burden. The comorbidities can be clustered into identifiable groups based on determinants of common human pathology that could help to create better phenotypes of patients with COPD. Regardless, understanding the relationships between COPD and its comorbidities from a cellular to a population level would enable future intervention that will ultimately result in improved outcomes.

Statement of Interest

D.M. Mannino has served on advisory boards for Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Sepracor, AstraZeneca, Novartis and Ortho Biotech, and has received research grants from AstraZeneca, GlaxoSmithKline, Novartis and Pfizer.

References

1. Global Strategy for the Diagnosis, Management, and Prevention of COPD. Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). 2011. Available from www.goldcopd.com Date last updated: February 21, 2012. Date last accessed: August 2012.
2. Celli BR, MacNee W, Agusti A. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
3. Celli BR, Halbert RJ, Isonaka S, *et al.* Population impact of different definitions of airway obstruction. *Eur Respir J* 2003; 22: 268–273.
4. Pellegrino R, Viegi G, Brusasco C, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
5. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007; 4: 502–506.
6. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007; 370: 765–773.
7. Franchi M. EFA Book on chronic obstructive pulmonary disease in Europe. Sharing and Caring. Brussels, European Federation of Airway Diseases, 2010.
8. Menezes AM, Perez-Padilla R, Jardim JR, *et al.* Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005; 366: 1875–1881.
9. Halbert RJ, Natoli JL, Gano A, *et al.* Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28: 523–532.
10. Buist AS, McBurnie MA, Vollmer WM, *et al.* International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370: 741–750.
11. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 1997; 349: 1498–1504.
12. Rycroft CE, Heyes A, Lanza L, *et al.* Epidemiology of chronic obstructive pulmonary disease: a literature review. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 457–494.
13. DiBonaventura Md., Paulose-Ram R., Su J., *et al.* The burden of chronic obstructive pulmonary disease among employed adults. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 211–219.
14. Dalal AA, Liu F, Riedel AA. Cost trends among commercially insured and medicare advantage-insured patients with chronic obstructive pulmonary disease: 2006 through 2009. *Int J Chron Obstruct Pulmon Dis* 2011; 6: 533–542.
15. National Heart, Lung, and Blood Institute. Fact book Fiscal Year 2006. Bethesda, NIH/NHLBI, 2007.
16. Rijcken B, Britton J. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir Monogr* 1998; 7: 74–83.
17. Nielsen R, Johannessen A, Benediktsdottir B, *et al.* Present and future costs of COPD in Iceland and Norway: results from the BOLD study. *Eur Respir J* 2009; 34: 850–857.
18. Mannino DM, Watt G, Hole D, *et al.* The natural history of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27: 627–643.
19. Divo M, Cote C, de Torres JP, *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155–161.
20. Decramer M, Rennard S, Troosters T, *et al.* COPD as a lung disease with systemic consequences – clinical impact, mechanisms, and potential for early intervention. *COPD* 2008; 5: 235–256.
21. Chatila WM, Thomashow BM, Minai OA, *et al.* Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 549–555.
22. Loscalzo J. System's biology and personalized medicine: a network approach to human disease. *Proc Am Thorac Soc* 2011; 8: 196–198.
23. Barnes PJ. COPD: inflammatory mechanisms and systemic consequences. *Eur Respir Monogr* 2013; 59: 13–27.
24. Mapel DW, Hurley JS, Frost FJ, *et al.* Health care utilization in chronic obstructive pulmonary disease: a case-control study in a health maintenance organization. *Arch Intern Med* 2000; 160: 2653–2658.

25. van Manen JG, Bindels PJ, IJzermans CJ, *et al.* Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol* 2001; 54: 287–293.
26. Soriano JB, Visick GT, Muellerova H, *et al.* Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; 128: 2099–2107.
27. Sidney S, Sorel M, Quesenberry CP Jr, *et al.* COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005; 128: 2068–2075.
28. Anecchino C, Rossi E, Fanizza C, *et al.* Prevalence of chronic obstructive pulmonary disease and pattern of comorbidities in a general population. *Int J Chron Obstruct Pulmon Dis* 2007; 2: 567–574.
29. Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962–969.
30. Cazzola M, Bettoncelli G, Sessa E, *et al.* Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration* 2010; 80: 112–119.
31. Agusti A, Calverley PMA, Celli B, *et al.* Characterization of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; 11: 122.
32. Feary JR, Rodrigues LC, Smith CJ, *et al.* Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke, a comprehensive analysis using data from primary care. *Thorax* 2010; 65: 956–962.
33. Curkendall SM, DeLuise C, Jones JK, *et al.* Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006; 16: 63–70.
34. Marin JM, Soriano JB, Carrizo SJ, *et al.* Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea, the overlap syndrome. *Am J Respir Crit Care Med* 2010; 182: 325–331.
35. Aryal S, Diaz-Guzman E, Mannino DM. Treatment options in asthma and chronic obstructive pulmonary diseases overlap syndrome. *Eur Respir Dis* 2011; 7: 101–105.
36. Pifarre R, Falguera M, Vicente-de-Vera C, *et al.* Characteristics of community-acquired pneumonia in patients with chronic obstructive pulmonary disease. *Respir Med* 2007; 101: 2139–2144.
37. Calverley PM, Anderson JA, Celli B, *et al.* TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
38. Lieberman D, Lieberman D, Gelfer Y, *et al.* Pneumonic vs nonpneumonic acute exacerbations of COPD. *Chest* 2002; 122: 1264–1270.
39. Tillie-Leblond I, Marquette CH, Perez T, *et al.* Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006; 144: 390–396.
40. Rutschmann OT, Cornuz J, Poletti PA, *et al.* Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax* 2007; 62: 121–125.
41. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32: 1371–1385.
42. Weitzenblum E, Chaouat A, Kessler R, *et al.* Overlap syndrome: obstructive sleep apnea in patients with chronic obstructive pulmonary disease. *Proc Am Thorac Soc Am Thorac Soc* 2008; 5: 237–241.
43. Lange P, Marott JL, Vestbo J, *et al.* Prediction of the clinical course of COPD using the new GOLD classification. A study of the general population. *Am J Respir Crit Care Med* 2012; 186: 975–981.
44. Barr RG, Celli BR, Mannino DM, *et al.* Comorbidities, patient knowledge, and disease management in a national sample of patients with COPD. *Am J Med* 2009; 122: 348–355.
45. Fabbri LM, Luppi F, Beghé B, *et al.* Complex chronic comorbidities of COPD. *Eur Respir J* 2008; 31: 204–212.
46. Lawes CM, Thornley S, Young R, *et al.* Statin use in COPD patients is associated with a reduction in mortality: a national cohort study. *Prim Care Respir J* 2012; 21: 35–40.
47. Patel AR, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. *Expert Rev Respir Med* 2011; 5: 647–662.
48. Schols AM, Soeters PB, Dingemans AM, *et al.* Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993; 147: 1151–1156.
49. Mannino DM, Aguayo SM, Petty TL, *et al.* Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003; 163: 1475–1480.
50. Wasswa-Kintu S, Gan WQ, Man SF, *et al.* Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax* 2005; 60: 570–575.
51. van Gestel YR, Hoeks SE, Sin DD, *et al.* COPD and cancer mortality: the influence of statins. *Thorax* 2009; 64: 963–967.
52. Maurer J, Rebbapragada V, Borson S, *et al.* Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 2008; 134: Suppl. 4, 43S–56S.
53. Hanania NA, Müllerova H, Locantore NW, *et al.* Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med*. 2011; 183: 604–611.
54. Incalzi RA, Corsonello A, Pedone C, *et al.* Chronic renal failure, a neglected comorbidity of COPD. *Chest* 2010; 137: 831–837.
55. Johnston AK, Mannino DM, Hagan GW, *et al.* Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort. *Thorax* 2008; 63: 599–605.
56. Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.

57. McGarvey LP, John M, Anderson JA, *et al.* Ascertainment of cause-specific mortality in COPD, operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; 62: 411–415.
58. Anthonisen NR, Connett JE, Enright PL, *et al.* Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002; 166: 333–339.
59. Kinnunen T, Saynajakangas O, Tuuponen T, *et al.* Impact of comorbidities on the duration of COPD patients' hospital episodes. *Respir Med* 2003; 97: 143–146.
60. Roberts CM, Stone RA, Lowe D, *et al.* Co-morbidities and 90-day outcomes in hospitalized COPD exacerbations. *COPD* 2011; 8: 354–361.
61. Lin PJ, Shaya FT, Scharf SM. Economic implications of comorbid conditions among Medicaid beneficiaries with COPD. *Respir Med* 2010; 104: 697–704.

Chapter 2

COPD: inflammatory mechanisms and systemic consequences



Peter J. Barnes

SUMMARY: COPD is associated with chronic inflammation predominantly affecting the lung parenchyma and peripheral airways, which results in largely irreversible and progressive airflow limitation. This inflammation is characterised by increased numbers of alveolar macrophages, neutrophils and T-lymphocytes (predominantly T-cytotoxic type 1, T-helper (Th) type 1 and Th17 cells) that are recruited from the circulation. These cells and structural cells, including epithelial and endothelial cells and fibroblasts, secrete a variety of pro-inflammatory mediators, including cytokines, chemokines, growth factors and lipid mediators. Oxidative stress plays a key role in driving this inflammation, even in ex-smokers, and may result in activation of the pro-inflammatory transcription factor nuclear factor- κ B, impaired antiprotease defences, DNA damage, cellular senescence, generation of autoantibodies and corticosteroid resistance though inactivation of histone deacetylase-2. The peripheral inflammation spills over into the circulation, resulting in systemic inflammation that may worsen comorbidities, such as cardiovascular diseases, diabetes and osteoporosis. Treatment of pulmonary inflammation, either by inhaled or oral anti-inflammatory therapies, may therefore have beneficial effects not only on the lung disease but also on associated comorbidities.

KEYWORDS: Autoantibody, cardiovascular disease, cytokine, diabetes, oxidative stress, systemic inflammation

Correspondence: P.J. Barnes,
National Heart and Lung Institute,
Imperial College School of Medicine,
Dovehouse Street, London SW3 6LY,
UK.
Email: p.j.barnes@imperial.ac.uk

Eur Respir Monogr 2013; 59: 13–27.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011112
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

COPD involves chronic inflammation of the lung, particularly in the peripheral airways and parenchyma, which increases during acute exacerbations. It is also associated with systemic inflammation, which may contribute or worsen several comorbidities. It is important to understand the nature of this inflammatory response in order to develop effective anti-inflammatory treatments for COPD in the future.

COPD is an obstructive disease of the lungs that slowly progresses over many decades, leading to death from respiratory failure unless patients die of comorbidities, such as cardiovascular disease

and lung cancer, before this stage. Although the commonest cause of COPD is chronic cigarette smoking, some patients, particularly in developing countries, develop the disease from inhalation of smoke from burning biomass fuels or other inhaled irritants [1]. However, only about 25% of smokers develop COPD, suggesting that there may be genetic, epigenetic or host factors that predispose to its development, although these have not yet been identified.

COPD as an inflammatory disease

The progressive airflow limitation in COPD is due to two major pathological processes: remodelling and narrowing of small airways, and destruction of the lung parenchyma with consequent destruction of the alveolar attachments of these airways as a result of emphysema. These pathological changes are due to chronic inflammation in the lung periphery, which increases as the disease progresses [2]. There is a characteristic pattern of inflammation with increased numbers of macrophages, T-lymphocytes and B-lymphocytes, together with increased numbers of neutrophils in the lumen [3–5]. The inflammatory response in COPD involves both innate and adaptive immune responses, which are linked through the activation of dendritic cells [6]. Multiple inflammatory mediators derived from inflammatory cells and structural cells of the airways and lungs are increased in COPD [7]. A similar pattern of inflammation and mediator expression is seen in smokers without airflow limitation, but in COPD this inflammation appears to be amplified and even further increased during acute exacerbations or when precipitated by bacterial or viral infection. The molecular basis for the amplification of inflammation is not yet fully understood but may be, at least in part, determined by genetic and epigenetic factors. Cigarette smoke and other irritants inhaled into the respiratory tract may activate surface macrophages and airway epithelial cells to release multiple chemotactic mediators, particularly chemokines, which attract circulating neutrophils, monocytes and lymphocytes into the lungs [8]. This inflammation persists even when smoking is stopped, suggesting that there are self-perpetuating mechanisms, although these have not yet been elucidated [9]. It is possible that memory T-cells, bacterial colonisation or autoimmunity may drive the persistent inflammation in COPD patients.

Differences from asthma

Although COPD and asthma involve pulmonary inflammation, there are marked differences in the site and nature of the inflammatory response [3]. In COPD, there is predominant involvement of the peripheral airways and lung parenchyma, whereas asthma involves inflammation in all airways (particularly proximal airways) but usually without involvement of the lung parenchyma [10]. In COPD there is narrowing of bronchioles, with fibrosis and infiltration of macrophages and T-lymphocytes, along with destruction of lung parenchyma and an increased number of macrophages and T-lymphocytes, with a greater increase in CD8+ than CD4+ T-helper (Th) cells [2]. Bronchial biopsies show similar changes with an infiltration of macrophages and CD8+ and CD4+ cells, whereas in asthma there is an increased number of mast cells, CD4+ cells (Th2 cells) and eosinophils. Bronchoalveolar lavage (BAL) fluid and induced sputum demonstrate a marked increase in macrophages and neutrophils, whereas in asthma there is an increase in eosinophils in some patients and neutrophils in others. In COPD, eosinophils are not prominent except during exacerbations or when patients have concomitant asthma [10]. The peripheral location of inflammation in COPD patients may explain why systemic inflammation is associated with COPD but not with asthma, where inflammation is localised to the airways so may not so easily access the systemic circulation. Although the inflammation in asthma and COPD is usually markedly different, in patients with severe asthma there are several features that are similar to the inflammation in COPD. For example, patients with severe asthma are more likely to have increased neutrophils, increased oxidative stress and increased expression of similar mediators to those of patients with COPD [3, 11].

Inflammatory cells

The inflammation of COPD lungs involves both innate immunity (neutrophils, macrophages, eosinophils, mast cells, natural killer (NK) cells, $\gamma\delta$ T-cells and dendritic cells) and adaptive immunity (T- and B-lymphocytes), but also involves the activation of structural cells, including airway and alveolar epithelial cells, endothelial cells and fibroblasts.

Epithelial cells

Epithelial cells are activated by cigarette smoke and other inhaled irritants, such as biomass fuel smoke, to produce inflammatory mediators, including tumour necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF) and CXCL8 (IL-8). Epithelial cells in small airways may also be an important source of transforming growth factor (TGF)- β , which then induces local fibrosis. Vascular endothelial growth factor (VEGF) appears to be necessary to maintain alveolar cell survival, and blockade of VEGF receptors (VEGFR2) in rats induces apoptosis of alveolar cells and an emphysema-like pathology [12]. Airway epithelial cells are also important in defense of the airways, with mucus production from goblet cells, and secretion of antioxidants, antiproteases and defensins. It is possible that cigarette smoke and other noxious agents may impair these responses of the airway epithelium, increasing susceptibility to infection. The airway epithelium in chronic bronchitis and COPD often shows squamous metaplasia, which may result from increased proliferation of basal airway epithelial cells, but the nature of the growth factors involved in epithelial cell proliferation, cell cycle and differentiation in COPD are not yet certain. Epithelial growth factor receptors (EGFRs) show increased expression in airway epithelial cells of COPD patients and may contribute to basal cell proliferation, resulting in squamous metaplasia and an increased risk of bronchial carcinoma [13].

Macrophages

Macrophages appear to play a key role in the pathophysiology of COPD and may orchestrate the inflammatory response (fig. 1) [14]. There is a marked increase (five- to 10-fold) in the number of macrophages in airways, lung parenchyma, BAL fluid and sputum in patients with COPD. Macrophages are localised to sites of alveolar wall destruction in patients with emphysema and there is a correlation between macrophage numbers in the parenchyma and severity of emphysema [15]. Macrophages may be activated by cigarette smoke extract to release inflammatory mediators, including TNF- α , CXCL1, CXCL8, CCL2 (monocyte chemoattractant protein-1), leukotriene (LT) B_4 and reactive oxygen species (ROS), providing a cellular mechanism that links smoking with inflammation in COPD. Alveolar macrophages also secrete elastolytic enzymes, including matrix metalloproteinase (MMP)-2, MMP-9, MMP-12,

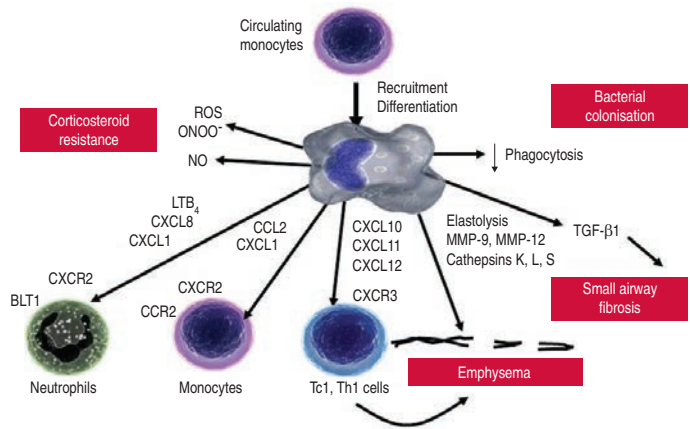


Figure 1. Central role of alveolar macrophages in COPD. Alveolar macrophages are derived from circulating monocytes which differentiate within the lung. They secrete many inflammatory proteins that may orchestrate the inflammatory process in COPD. Neutrophils may be attracted by CXCL8, CXCL1 and leukotriene (LT) B_4 , monocytes by CCL2, and T-cytotoxic (Tc) type 1 and T-helper (Th) type 1 lymphocytes by CXCL10, CXCL11 and CXCL12. Release of elastolytic enzymes, including matrix metalloproteinases (MMP) and cathepsins, causes elastolysis contributing to emphysema together with Tc-cells. Release of transforming growth factor (TGF)- β 1 may induce fibrosis of small airways. Macrophages generate reactive oxygen species (ROS) and nitric oxide (NO), which together form peroxynitrite (ONOO $^-$) and may contribute to corticosteroid resistance. Defective bacterial phagocytosis may lead to bacterial colonisation. BLT: LTB $_4$ receptor.

cathepsins K, L and S, and neutrophil elastase taken up from neutrophils [16]. Alveolar macrophages from patients with COPD secrete more inflammatory proteins and have a greater elastolytic activity at baseline than those from normal smokers; this is further increased by exposure to cigarette smoke [16]. Macrophages demonstrate this difference even when maintained in culture for 3 days and therefore appear to be intrinsically different from the macrophages of normal smokers and nonsmoking normal control subjects [16]. The predominant elastolytic enzyme secreted by alveolar macrophages in COPD patients is MMP-9. Most of the inflammatory proteins that are upregulated in COPD macrophages are regulated by the transcription factor nuclear factor (NF)- κ B, which is activated in the alveolar macrophages of COPD patients, particularly during exacerbations [17]. The increased numbers of macrophages in the lungs of smokers and COPD patients is due to increased recruitment of monocytes from the circulation in response to the monocyte-selective chemokines CCL2 and CXCL1, which are increased in the sputum and BAL fluid of patients with COPD [18]. Monocytes from patients with COPD show a greater chemotactic response to CXCL1 than cells from normal smokers and nonsmokers, but this is not explained by an increase in its receptor CXCR2 [19]. Interestingly, while all monocytes express CCR2, the receptor for CCL2, only ~30% of monocytes express CXCR2. Macrophages also release CXCL9, CXCL10 and CXCL11, which are chemotactic for CD8+ T-cytotoxic (Tc) type 1 and CD4+ Th1 cells, *via* interaction with the chemokine receptor CXCR3 expressed on these cells [20]. Macrophages from COPD patients release more inflammatory proteins than macrophages from normal smokers and nonsmokers, indicating increased activation [21].

Corticosteroids are ineffective in suppressing inflammation, including cytokines, chemokines and proteases, in patients with COPD [22]. *In vitro*, the release of CXCL8, TNF- α and MMP-9 by macrophages from normal subjects and normal smokers are inhibited by corticosteroids, whereas corticosteroids are ineffective in macrophages from patients with COPD [21]. The reasons for resistance to corticosteroids in COPD may be the marked reduction in activity of histone deacetylase (HDAC)2 [23, 24], which is recruited to activated inflammatory genes by glucocorticoid receptors to switch off inflammatory genes. The reduction in HDAC activity in macrophages is correlated with increased secretion of cytokines like TNF- α and CXCL8 and reduced response to corticosteroids. The reduction of HDAC2 activity on COPD patients may be mediated through oxidative stress and peroxynitrite formation [25].

Both alveolar macrophages and monocyte-derived macrophages from COPD patients also show reduced phagocytic uptake of bacteria and this may be a factor in determining chronic colonisation of the lower airways by bacteria such as *Haemophilus influenzae* or *Streptococcus pneumoniae* [26]. COPD macrophages are also defective in taking up apoptotic cells and this may contribute to the failure to resolve inflammation in COPD [27]. The nature of this defect in phagocytosis is not fully understood but appears to be due to a defect in microtubular function that is required for phagocytosis rather than any abnormality of recognition of the phagocytosed particles [28]. The bacterial colonisation of the lower airways may predispose to increased acute exacerbations and also to the increased risk of developing community-acquired pneumonia in COPD patients [29].

Neutrophils

Increased numbers of activated neutrophils are found in the sputum and BAL fluid of patients with COPD [30], although few neutrophils are seen in the airway wall and lung parenchyma, probably reflecting their rapid transit through these tissues. Neutrophil numbers in induced sputum correlate with COPD disease severity [30]. Smoking has a direct stimulatory effect on granulocyte production and release from the bone marrow and survival in the respiratory tract, possibly mediated by GM-CSF and granulocyte colony-stimulating factor released from lung macrophages. Neutrophil recruitment to the airways and parenchyma involves adhesion to endothelial cells and E-selectin, which is upregulated on endothelial cells in the airways of COPD patients. Adherent neutrophils migrate into the respiratory tract under the direction of various neutrophil chemotactic factors, including LTB₄, CXCL8 and the related CXC chemokines CXCL1

(GRO- α) and CXCL5 (ENA-78), which are increased in COPD airways [18]. These chemotactic mediators may be derived from alveolar macrophages, T-cells and epithelial cells, but the neutrophil itself may be a major source of CXCL8. Neutrophils recruited to the airways of COPD patients are activated as there are increased concentrations of granule proteins, such as myeloperoxidase and human neutrophil lipocalin, in the sputum supernatant [31]. Neutrophils secrete serine proteases, including neutrophil elastase, cathepsin G and proteinase-3, as well as MMP-8 and MMP-9, which may contribute to alveolar destruction. Airway neutrophilia is linked to mucus hypersecretion as neutrophil elastase, cathepsin G and proteinase-3 are potent stimulants of mucus secretion from submucosal glands and goblet cells. There is a marked increase in neutrophil numbers in the airways in acute exacerbations of COPD accounting for the increased purulence of sputum. This may reflect increased production of neutrophil chemotactic factors, including LTB₄ and CXCL8 [32, 33].

Dendritic cells

Dendritic cell plays a central role in the initiation of the innate and adaptive immune response and provide a link between them. The airways and lungs contain a rich network of dendritic cells that are localised near the surface, so that they are ideally located to signal the entry of foreign substances that are inhaled. Dendritic cells can activate a variety of other inflammatory and immune cells, including macrophages, neutrophils, and T- and B-lymphocytes, so dendritic cells may play an important role in the pulmonary response to cigarette smoke and other inhaled noxious agents. Dendritic cells appear to be activated in the lungs of COPD patients [34].

T-lymphocytes

There is an increase in the total numbers of T-lymphocytes in the lung parenchyma, peripheral and central airways of patients with COPD, with the greater increase in CD8+ rather than CD4+ cells [2, 20]. There is a correlation between the numbers of T-cells and the amount of alveolar destruction and the severity of airflow obstruction. Furthermore, the only significant difference in the inflammatory cell infiltrate in asymptomatic smokers and smokers with COPD is an increase in T-cells, mainly CD8+ (Tc1), in patients with COPD. There is also an increase in the absolute number of CD4+ (Th1) T-cells, albeit in smaller numbers, in the airways of smokers with COPD and these cells express activated signal transducer and activator of transcription (STAT)-4, a transcription factor that is essential for activation and commitment of the Th1 lineage [35]. CD4+ Th17 cells, which secrete IL-17A and IL-22, are also increased in airways of COPD patients and may play a role in orchestrating neutrophilic inflammation [36, 37]. Th17 cells may be regulated by IL-6 and IL-23 released from alveolar macrophages. CD4+ and CD8+ T-cells in the lung of COPD patients show increased expression of CXCR3, a receptor activated by the chemokines CXCL9, CXCL10 and CXCL11, all of which are increased in COPD [38]. There is increased expression of CXCL10 by bronchiolar epithelial cells and this could contribute to the accumulation of CD4+ and CD8+ T-cells, which preferentially express CXCR3 [39]. CD8+ cells are typically increased in airway infections and it is possible that the chronic bacterial colonisation of the lower respiratory tract of COPD patients is responsible for this inflammatory response.

Autoimmune mechanisms may also be involved. Cigarette-induced lung injury may uncover previously sequestered autoantigens or cigarette smoke itself may damage lung interstitial and structural cells, making them antigenic [4]. Oxidative stress may result in the formation of carbonylated proteins that are antigenic, and several anti-carbonylated protein antibodies have been found in the circulation of COPD patients, particularly in severe disease [40]. Antiendothelial antibodies have also been detected [40, 41]. Autoantibodies may cause cell damage through the binding of complement, which is increased in the lungs of COPD patients.

CD8+ cells cause cytolysis and apoptosis of alveolar epithelial cells through release of perforins, granzyme B and TNF- α , and there is an association between CD8+ cells and apoptosis of alveolar cells in emphysema [42]. There is evidence of immunological senescence in COPD with increased

numbers of T-cells with no expression of the co-stimulatory receptor CD28 (CD4/CD28^{null} and CD8/CD28^{null} cells) and these cells release increased amounts of perforins and granzyme B [43, 44].

Mediators of inflammation

Many inflammatory mediators have now been implicated in COPD, including lipids, free radicals, cytokines, chemokines and growth factors [7]. These mediators are derived from inflammatory and structural cells in the lung and interact with each other in a complex manner. Because so many mediators are involved, it is unlikely that blocking a single mediator will have much clinical impact. Similar mediators that are found in the lungs of COPD patients may also be increased in the circulation and this systemic inflammation may underlie and potentiate comorbidities, as discussed below.

Lipid mediators

The profile of lipid mediators in exhaled breath condensates of patients with COPD shows an increase in prostaglandins (PGs) and LTs [45]. There is a significant increase in PGE₂ and PGF_{2α} and an increase in LTB₄ but not in cysteinyl-LTs. This is a different pattern to that seen in asthma, in which increases in thromboxane and cysteinyl-LTs have been shown. The increased production of prostanoids in COPD is likely to be secondary to the induction of cyclo-oxygenase (COX)2 by inflammatory cytokines and increased expression of COX2 has been described in the alveolar macrophages of COPD patients. LTB₄ concentrations are also increased in induced sputum and further increased in sputum and exhaled breath condensate during acute exacerbations [32]. LTB₄ is a potent chemoattractant of neutrophils, acting through high-affinity BLT₁-receptors. A BLT₁-receptor antagonist reduces the neutrophil chemotactic activity of sputum by approximately 25% [46]. Recently, BLT₁-receptors have been identified on T-lymphocytes and there is evidence that LTB₄ is also involved in recruitment of T-cells [47].

Cytokines

Cytokines are the mediators of chronic inflammation and several have been implicated in COPD [11, 48]. There is an increase in concentration of TNF-α in induced sputum in stable COPD with a further increase during exacerbations [30, 33]. TNF-α production from peripheral blood monocytes is also increased in COPD patients and has been implicated in the cachexia and skeletal muscle apoptosis found in some patients with severe disease. TNF-α is a potent activator of NF-κB and this may amplify the inflammatory response. Unfortunately, anti-TNF therapies have not proved to be effective in COPD patients and may have serious adverse effects. IL-1β and IL-6 are other pro-inflammatory cytokines that may amplify the inflammation in COPD and may be important for systemic circulation. IL-1β and the related cytokine IL-18 may be produced *via* the activation of the NLRP3 inflammasome by cellular stress including bacterial infections [49]. IL-17 and other Th17 cytokines are also increased in COPD sputum and airways and may play a role in orchestrating neutrophilic inflammation in the lungs [36, 50].

Chemokines

Several chemokines have been implicated in COPD and have been of particular interest as chemokine receptors are G-protein coupled receptors, for which small-molecule receptor antagonists have now been developed [8]. CXCL8 concentrations are increased in induced sputum of COPD patients and increase further during exacerbations [30, 33]. CXCL8 is secreted from macrophages, T-cells, epithelial cells and neutrophils. CXCL8 activates neutrophils *via* the low-affinity specific receptor CXCR1 and is chemotactic for neutrophils *via* the high-affinity receptor CXCR2, which is also activated by related CXC chemokines, such as CXCL1. CXCL1 concentrations are markedly elevated in the sputum and BAL fluid of COPD patients and this chemokine may be more important as a chemoattractant than CXCL8, acting *via* CXCR2, which is

expressed on neutrophils and monocytes [18]. CXCL1 induces significantly more chemotaxis of monocytes of COPD patients compared to those of normal smokers and this may reflect increased turnover and recovery of CXCR2 in monocytes of COPD patients [19]. CXCL5 shows a marked increase in expression in airway epithelial cells during exacerbations of COPD and this is accompanied by a marked upregulation of epithelial CXCR2.

CCL2 is increased in concentration in COPD sputum and BAL fluid [18] and plays a role in monocyte chemotaxis *via* activation of CCR2. CCL2 appears to cooperate with CXCL1 in recruiting monocytes into the lungs. The chemokine CCL5 (RANTES) is also expressed in the airways of COPD patients during exacerbations, and activates CCR5 on T-cells and CCR3 on eosinophils, which may account for the increased eosinophils and T-cells in the wall of large airways that have been reported during exacerbations of chronic bronchitis. As previously discussed, CXCR3 is upregulated on the Tc1 and Th1 cells of COPD patients with increased expression of its ligands CXCL9, CXCL10 and CXCL11 [38].

Growth factors

TGF- β 1 is expressed in the alveolar macrophages and airway epithelial cells of COPD patients and is released from the epithelial cells of small airways. TGF- β is released in a latent form and activated by various factors, including MMP-9 and oxidative stress. TGF- β may play an important role in the characteristic peribronchiolar fibrosis of small airways, either directly or through the release of connective tissue growth factor. Alveolar macrophages produce TGF- α in greater amounts than TGF- β and this may be a major endogenous activator of EGFR, which plays a key role in regulating mucus secretion in response to many stimuli, including cigarette smoke. Cigarette smoke activates TNF- α -converting enzyme on airway epithelial cells, which results in the shedding of TGF- α and the activation of EGFR, resulting in increased mucus secretion [51].

VEGF is a major regulator of vascular growth and is likely to be involved in the pulmonary vascular remodelling that occurs as a result of hypoxic pulmonary vasoconstriction in severe COPD. There is increased expression of VEGF in the pulmonary vascular smooth muscle of patients with mild and moderate COPD but, paradoxically, a reduction in expression in severe COPD with emphysema. Inhibition of VEGF receptors using a selective inhibitor induces apoptosis of alveolar endothelial cells in rats, resulting in emphysema, and this appears to be driven by oxidative stress. In addition, VEGF is also an important pro-inflammatory cytokine produced by epithelial and endothelial cells, macrophages and activated T-cells, which acts by increasing endothelial cell permeability, by inducing expression of endothelial adhesion molecules and *via* its ability to act as a monocyte chemoattractant. VEGF is probably an intermediary between cell-mediated immune inflammation and the associated angiogenesis reaction.

Proteases

The increase in elastase activity in COPD patients may contribute to the development of emphysema and to neutrophilic inflammation through the generation of chemotactic peptides such as Pro-Gly-Pro (matrikines). Human neutrophil elastase not only has elastolytic activity but is also a potent stimulant of mucus secretion in the airways. MMP-9 appears to be the predominant elastolytic enzyme in COPD and is secreted from macrophages, neutrophils and epithelial cells. MMP-9 causes elastolysis but also stimulates neutrophilic inflammation through the generation of *N*-acetyl-Pro-Gly-Pro [52]. Interestingly, MMP-9 activation has been implicated in skin wrinkling and in arterial stiffness, which are indicators of COPD comorbidity.

Oxidative stress

Oxidative stress occurs when ROS are produced in excess of the antioxidant defence mechanisms and result in harmful effects, including damage to lipids, proteins and DNA. Oxidative stress is a

critical feature in COPD [53]. Inflammatory and structural cells, including neutrophils, macrophages and epithelial cells, that are activated in the airways of patients with COPD produce ROS. Superoxide anions ($O_2^{\cdot-}$) are generated by reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and converted to hydrogen peroxide (H_2O_2) by superoxide dismutases (SODs). H_2O_2 is then dismutated to water by catalase. $O_2^{\cdot-}$ and H_2O_2 may interact in the presence of free iron to form the highly reactive hydroxyl radical ($\cdot OH$). $O_2^{\cdot-}$ may also combine with nitric oxide (NO) to form $ONOO^-$, which also generates $\cdot OH$. Oxidative stress leads to the oxidation of arachidonic acid and the formation of a new series of prostanoid mediators called isoprostanes, which may exert significant functional effects, including bronchoconstriction and plasma exudation [54]. $ONOO^-$ is also increased in the breath of COPD patients [55]. NO may be increased in the peripheral lung of COPD patients and appears to be linked to increased expression of inducible and neural NO synthases (NOS2 and NOS1, respectively) [55, 56].

The normal production of oxidants is counteracted by several antioxidant mechanisms in the human respiratory tract, including catalase, SODs and glutathione, formed by the enzymes γ -glutamyl cysteine synthetase and glutathione synthetase. In the lung, intracellular antioxidants are expressed at relatively low levels and are not induced by oxidative stress, whereas the major antioxidants are extracellular. Extracellular antioxidants, particularly glutathione peroxidase, are markedly upregulated in response to cigarette smoke and oxidative stress. Extracellular antioxidants also include the dietary antioxidants vitamin C (ascorbic acid) and vitamin E (α -tocopherol), uric acid, lactoferrin, and extracellular SOD (SOD3), which is highly expressed in human lung. Most antioxidants are regulated by the transcription factor nuclear erythroid-2 related factor-2 (Nrf2), which is activated by oxidative stress. However, in COPD lungs and cells, Nrf2 is not appropriately activated [57, 58] and this may be related to increased acetylation due to decreased HDAC2 [58].

ROS have wide-ranging effects on the airways and parenchyma and increase the inflammatory response (fig. 2). ROS activate NF- κ B, which switches on multiple inflammatory genes resulting in amplification of the inflammatory response. Oxidative stress results in the activation of histone acetyltransferase activity, which opens up the chromatin structure and is associated with increased transcription of multiple inflammatory genes [59]. Oxidative stress may also impair the function of antiproteases such as α_1 -antitrypsin and secretory leukocyte peptidase inhibitor (SLPI), and thereby accelerates the breakdown of elastin in lung parenchyma. Oxidative stress markedly reduces HDAC2 activity and expression, through activation of phosphoinositide-3-kinase- δ

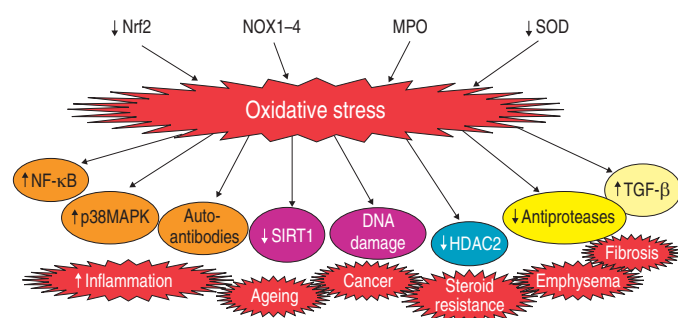


Figure 2. Oxidative stress in COPD. Oxidative stress may be increased in COPD by a reduction in the transcription factor nuclear erythroid-2 related factor-2 (Nrf2), activation of NADPH oxidases (NOX), myeloperoxidase (MPO) and reduced superoxide dismutase (SOD). Oxidative stress is a key driving mechanisms in COPD through activation of the pro-inflammatory transcription factor nuclear factor (NF)- κ B, p38 mitogen-activated protein kinase (MAPK), generation of autoantibodies to carbonylated proteins, reduced sirtuin-1 (SIRT1), DNA damage, reduced histone deacetylase (HDAC)2, reduced antiproteases and increased transforming growth factor (TGF)- β .

and $ONOO^-$ -induced nitration of tyrosine residues. This amplifies inflammation further and prevents corticosteroids from inactivating activated inflammatory genes. Through similar mechanisms, oxidative stress reduces the expression and activity of sirtuin-1, a key repair molecule that is implicated in ageing. The reduction in sirtuin-1 in COPD lungs and cells may underlie the accelerated ageing response seen in COPD [60]. Oxidative stress may also predispose to lung cancer, through the activation of growth factors and *via* DNA damage [61]. Oxidative stress leads to formation of carbonylated proteins, which may be antigenic and stimulate the development of autoantibodies in COPD patients [40].

There is also evidence of systemic oxidative stress in COPD patients with an increase in lipid peroxidation products and decreased antioxidant capacity. Furthermore, circulating neutrophils release more ROS than neutrophils from normal smokers and nonsmokers [62]. Systemic oxidative stress increases further during acute exacerbations [63].

Systemic inflammation in COPD

Patients with COPD, particularly when the disease is severe and during exacerbations, have evidence of systemic inflammation, measured either as increased circulating cytokines, chemokines and acute-phase proteins, or as abnormalities in circulating cells (fig. 3) [64, 65]. Smoking itself may cause systemic inflammation (for example, an increased total leukocyte count) but in COPD patients, the degree of systemic inflammation is greater. It is still uncertain whether these systemic markers of inflammation are a “spill-over” from inflammation in the peripheral lung, a parallel abnormality or related to some comorbid disease that then has effects on the lung. In any case, the components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid diseases. In a large population study, systemic inflammation (increased C-reactive protein (CRP), fibrinogen and leukocytes) was associated with a two- to four-fold increased risk of cardiovascular disease, diabetes, lung cancer and pneumonia but not with depression [66]. Using six inflammatory markers (CRP, IL-6, CXCL8, fibrinogen, TNF- α and leukocytes), 70% of COPD patients had some components of systemic inflammation and 16% had persistent inflammation [67]. Patients with persistent systemic inflammation had increased mortality and more frequent exacerbations. Systemic inflammation appears to relate to accelerated decline in lung function and is increased further during exacerbations [68].

Acute-phase proteins

CRP is an acute-phase protein that is increased in the plasma of COPD patients, particularly during acute infective exacerbations. In stable COPD, plasma concentrations are related to all-cause mortality in mild-to-moderate patients [69], but not in severe or very severe patients [70]. However, although CRP is related to forced expiratory volume in 1 second (FEV₁) in cross-sectional studies, there is no association with progressive

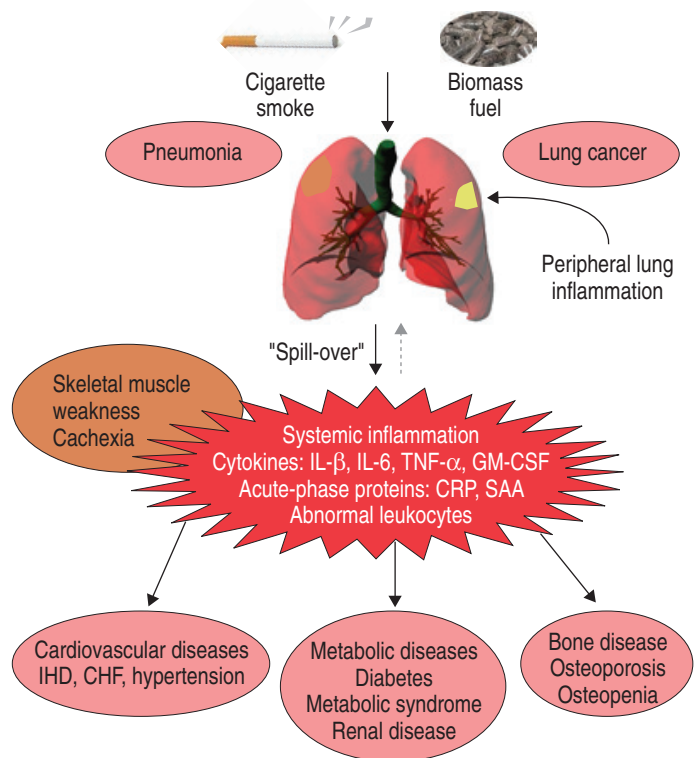


Figure 3. Proposed model of systemic inflammation and comorbidities in COPD. Patients with COPD have peripheral lung inflammation that may “spill over” into the systemic circulation, leading to skeletal muscle weakness and cachexia, and increasing propensity to cardiovascular, metabolic and bone diseases. There is an increase in circulating cytokines, including interleukin (IL)-1 β , IL-6, tumour necrosis factor (TNF)- α and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as acute-phase proteins, such as C-reactive protein (CRP) and serum amyloid A (SAA), and abnormal leukocytes. Peripheral lung inflammation may also increase the risk of developing lung cancer and community-acquired pneumonia. IHD: ischaemic heart disease; CHF: congestive heart failure.

decline of FEV₁ in longitudinal studies [71]. CRP is also increased in exacerbations of COPD, whether due to viral or bacterial causes [68], and a high concentration of CRP 2 weeks after an exacerbation predicts the likelihood of recurrent exacerbation [72]. CRP in plasma is produced by the liver in response to circulating IL-6 and, therefore, may be a biomarker of systemic inflammation rather than directly contributing to comorbid diseases.

Plasma fibrinogen concentrations are increased in COPD patients with frequent exacerbations [63, 73]. An elevated plasma fibrinogen in a population is related to worse FEV₁ and increased risk of hospitalisation for COPD [74].

Serum amyloid A (SAA) is another acute-phase protein released by circulating pro-inflammatory cytokines from the liver but, unlike CRP, also from inflamed tissue. It has been identified by proteomic analysis of plasma as showing an increase during acute exacerbations of COPD and its concentrations are correlated with the severity of exacerbations [75]. SAA binds to Gram-negative bacteria and is part of the innate defence mechanism against bacterial infections, but it also has pro-inflammatory effects, including activation of epithelial cells, neutrophils, monocytes and Th17 cells to release pro-inflammatory mediators and inhibit the effects of anti-inflammatory lipoxins [76]. SAA activates Toll-like receptor 2, resulting in activation of NF- κ B [77].

Surfactant protein (SP)-D is a glycoprotein member of the collectin family, is secreted mainly by type II pneumocytes and club cells (Clara cells), and plays a role in innate defence against microorganisms. Serum SP-D concentrations are increased in smokers and in patients with COPD but are weakly correlated to disease severity [78]. Serum SP-D is further increased transiently during exacerbations. Serum SP-D is also increased in other lung diseases, including asthma, pulmonary fibrosis and pneumonia, so it lacks specificity. While SP-D in serum is increased in COPD, its concentrations are reduced in BAL fluid, suggesting that it may translocate from the lung to the systemic circulation [79]. The reduced concentration of SP-D in BAL fluid may be due to oxidative damage of the quaternary structure so that it is not detectable by immunoassay.

Cytokines

IL-6 is consistently increased in the systemic circulation of COPD patients, particularly during exacerbations, and may account for the increase in circulating acute-phase proteins such as CRP and SAA [80]. The functional effects of circulating IL-6, apart from increasing acute-phase proteins, are not certain, but there is evidence that it may be associated with skeletal muscle weakness. In an ageing population with or without airway obstruction, plasma IL-6 concentrations are related to decreased muscle strength measured by quadriceps strength and exercise capacity [81]. In rats, infusion of IL-6 induces both cardiac failure and skeletal muscle weakness [82]. Elevated circulating IL-6 concentrations are associated with several comorbid diseases, including ischaemic heart disease, diabetes and osteoporosis.

Plasma TNF- α and its soluble receptor (sTNFR75) are increased in COPD patients [83], and TNF- α is released from circulating cells in COPD patients with cachexia [84]. Circulating TNF- α appears to be related, at least in part, to hypoxaemia [85]. Increased systemic TNF- α has been implicated as a mechanism of cachexia and skeletal muscle weakness in COPD patients. Chronic administration of TNF- α in animals results in cachexia, anaemia, leukocytosis and infiltration of neutrophils into organs such as the heart, liver and spleen [86].

IL-1 β has also been linked to cachexia but increased plasma concentrations or decreased concentrations of its endogenous antagonist IL-1 receptor antagonist have not been found in COPD, although there is an association between COPD and a polymorphism of the IL-1 β gene [83].

CXCL8 and other CXC chemokines play an important role in neutrophil and monocyte recruitment in COPD patients. Circulating CXCL8 concentrations are also increased in COPD patients and have been related to muscle weakness [87].

Circulating cells

The blood leukocyte count was a predictor of total mortality independent of cigarette smoking in a large population-based study [88, 89]. Abnormalities in circulating leukocytes may have effects on organs other than the lung and, therefore, may contribute to comorbidities. An integral part of the systemic inflammatory response is activation of the bone marrow, which results in the release of leukocytes and platelets into the circulation. While circulating neutrophil numbers are not usually increased in stable COPD, there is an inverse correlation between neutrophil numbers in the circulation and FEV₁ [90]. There may be an increased turnover of neutrophils in smokers since neutrophils appear to marginate in the pulmonary circulation and are then replaced in the periphery by increased bone marrow production [91]. In rabbits, IL-6 and GM-CSF increase production from the bone marrow in association with downregulation of L-selectin on circulating neutrophils and promoting preferential sequestration in the pulmonary microcirculation [92, 93]. Neutrophils from COPD patients also show enhanced production of ROS in response to stimulatory agents [94]. Although no difference in spontaneous apoptosis of circulating neutrophils has been reported in COPD patients compared with normal smokers, there is a reduction in L-selectin and an increase in CD11b expression [95].

Circulating T-cells show increased numbers of CD4⁺ CD28^{null} and CD8⁺ CD28^{null} cells that are typical of immune senescence, and these T-cells contain and release increased amounts of perforins and granzyme B [43, 44]. Circulating $\gamma\delta$ T-cells are increased in normal smokers but not in COPD patients [96].

A reduction of cytotoxic and phagocytic function of circulating NK cells has been reported in COPD [97, 98]. There is a reduction in the number of invariant NK T-cells in the circulation [99].

Does “spill-over” from the lungs account for systemic inflammation in COPD?

It is generally assumed that inflammation in peripheral lung is able to reach the systemic circulation and, thus, account for the systemic inflammation found in COPD. SP-D is produced mainly in type 2 pneumocytes and club cells in the lung periphery, and is increased in the serum of COPD patients, although this increase is also seen in other pulmonary inflammatory diseases. Inhaled proteins, such as insulin, reach the systemic circulation [100]. Inhalation of particulates (particulate matter <10 μ m in diameter) during an episode of acute air pollution leads to activation of alveolar macrophages to produce cytokines, including IL-1 β , IL-6 and GM-CSF, which reach the systemic circulation to trigger a bone marrow response, with increased leukocytes and platelets [101]. It is also possible that inhaled small particles (such as nanoparticles) may reach the systemic circulation to induce an inflammatory response. The cytokines TNF- α , IL-1 β , IL-6, GM-CSF and CXCL8 are increased in the sputum, BAL fluid and circulation of COPD patients, suggesting a similar inflammatory profile. However, there is not a good relationship between concentrations in the sputum and serum [102]. This may be explained by metabolism of cytokines in the circulation and binding to soluble receptors. Furthermore, the concentrations in induced sputum may reflect inflammation in conducting airways, whereas overspill of inflammatory mediators may occur in the lung periphery. A further complication is that a cytokine released from the lung into the systemic circulation may then activate circulating cells to produce more of the same cytokines as well as additional cytokines.

Lung cancer and inflammation

The incidence of lung cancer amongst patients with COPD is over 10 times higher than in smokers without airway obstruction [103] and COPD is common amongst patients with lung cancer [104]. A plausible mechanism to account for this association is the tumorigenic effects of chronic inflammation, as in other cancers such as colon cancer that is associated with inflammatory bowel disease. There are several molecular mechanisms that may explain how chronic inflammation may

increase cancer risk [61]. EGFR shows increased expression on airway epithelial cells in COPD patients, has been associated with lung cancer cells and may be stimulated by ligands, such as epidermal growth factor and TNF- α , as well as indirectly *via* oxidative stress and neutrophil elastase. Oxidative stress also leads to DNA damage in the peripheral lung, whereas in normal smokers this damage is repaired by efficient DNA repair mechanisms, as measured by the increased number of apurinic/apyrimic (AP) sites. However, in COPD lungs, despite DNA damage by oxidative stress, AP sites are not increased and the double-stranded DNA repair molecule Ku86 is reduced [105].

Implications for therapy

There is a great unmet need for safe and effective anti-inflammatory treatments for COPD [106]. If systemic inflammation is derived from peripheral lung inflammation, inhaled anti-inflammatory treatments may reduce spill-over and, thus, systemic inflammation. If systemic inflammation is causally related to worsening of comorbidities, then this may in turn ameliorate comorbid diseases. At present, there are no effective inhaled anti-inflammatory treatments as corticosteroids are ineffective against the inflammation of COPD, so it is not certain how systemic inflammation and comorbidities would be affected. The only oral anti-inflammatory treatment currently on the market is the phosphodiesterase-4 inhibitor roflumilast, although the dose is limited by side-effects and no consistent reduction in systemic inflammatory biomarkers has been reported. However, in newly diagnosed diabetic patients, roflumilast in the same dose that reduces lung inflammation improved control of diabetes as measured by a reduction in glycated haemoglobin, reduced blood glucose and increased C-peptide [107]. Systemic anti-inflammatory treatments may, therefore, treat not only pulmonary inflammation but also the comorbidities of COPD, such as diabetes, ischaemic heart disease and osteoporosis.

Statement of Interest

None declared.

References

1. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009; 374: 733–743.
2. Hogg JC, Chu F, Utokaparch S, *et al*. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 2645–2653.
3. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Immunol Rev* 2008; 8: 183–192.
4. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. *N Engl J Med* 2009; 360: 2445–2454.
5. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. *Lancet* 2011; 378: 1015–1026.
6. Van Pottelberge GR, Bracke KR, Joos GF, *et al*. The role of dendritic cells in the pathogenesis of COPD: liaison officers in the front line. *COPD* 2009; 6: 284–290.
7. Barnes PJ. Mediators of chronic obstructive pulmonary disease. *Pharm Rev* 2004; 56: 515–548.
8. Donnelly LE, Barnes PJ. Chemokine receptors as therapeutic targets in chronic obstructive pulmonary disease. *Trends Pharmacol Sci* 2006; 27: 546–553.
9. Gamble E, Grootendorst DC, Hattotuwa K, *et al*. Airway mucosal inflammation in COPD is similar in smokers and ex-smokers: a pooled analysis. *Eur Respir J* 2007; 30: 467–471.
10. Fabbri LM, Romagnoli M, Corbetta L, *et al*. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 167: 418–424.
11. Barnes PJ. Cytokine networks in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 2008; 118: 3546–3556.
12. Petrache I, Natarajan V, Zhen L, *et al*. Ceramide upregulation causes pulmonary cell apoptosis and emphysema-like disease in mice. *Nat Med* 2005; 11: 491–498.
13. de Boer WI, Hau CM, van Schadewijk A, *et al*. Expression of epidermal growth factors and their receptors in the bronchial epithelium of subjects with chronic obstructive pulmonary disease. *Am J Clin Pathol* 2006; 125: 184–192.
14. Barnes PJ. Macrophages as orchestrators of COPD. *J COPD* 2004; 1: 59–70.
15. Meshi B, Vitalis TZ, Ionescu D, *et al*. Emphysematous lung destruction by cigarette smoke. The effects of latent adenoviral infection on the lung inflammatory response. *Am J Respir Cell Mol Biol* 2002; 26: 52–57.

16. Russell RE, Thorley A, Culpitt SV, *et al.* Alveolar macrophage-mediated elastolysis: roles of matrix metalloproteinases, cysteine, and serine proteases. *Am J Physiol Lung Cell Mol Physiol* 2002; 283: L867–L873.
17. Caramori G, Romagnoli M, Casolari P, *et al.* Nuclear localisation of p65 in sputum macrophages but not in sputum neutrophils during COPD exacerbations. *Thorax* 2003; 58: 348–351.
18. Traves SL, Culpitt S, Russell REK, *et al.* Elevated levels of the chemokines GRO- α and MCP-1 in sputum samples from COPD patients. *Thorax* 2002; 57: 590–595.
19. Traves SL, Smith SJ, Barnes PJ, *et al.* Specific CXC but not CC chemokines cause elevated monocyte migration in COPD: a role for CXCR2. *J Leukoc Biol* 2004; 76: 441–450.
20. Grumelli S, Corry DB, Song LX, *et al.* An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. *PLoS Med* 2004; 1: 75–83.
21. Culpitt SV, Rogers DF, Shah P, *et al.* Impaired inhibition by dexamethasone of cytokine release by alveolar macrophages from patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 167: 24–31.
22. Keatings VM, Jatakanon A, Worsdell YM, *et al.* Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997; 155: 542–548.
23. Ito K, Ito M, Elliott WM, *et al.* Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *N Engl J Med* 2005; 352: 1967–1976.
24. Ito K, Yamamura S, Essilfie-Quaye S, *et al.* Histone deacetylase 2-mediated deacetylation of the glucocorticoid receptor enables NF- κ B suppression. *J Exp Med* 2006; 203: 7–13.
25. Barnes PJ. Role of HDAC2 in the pathophysiology of COPD. *Ann Rev Physiol* 2009; 71: 451–464.
26. Taylor AE, Finney-Hayward TK, Quint JK, *et al.* Defective macrophage phagocytosis of bacteria in COPD. *Eur Respir J* 2010; 35: 1039–1047.
27. Hodge S, Hodge G, Scicchitano R, *et al.* Alveolar macrophages from subjects with chronic obstructive pulmonary disease are deficient in their ability to phagocytose apoptotic airway epithelial cells. *Immunol Cell Biol* 2003; 81: 289–296.
28. Donnelly LE, Barnes PJ. Defective phagocytosis in airways disease. *Chest* 2012; 141: 1055–1062.
29. Mullerova H, Chigbo C, Hagan GW, *et al.* The natural history of community-acquired pneumonia in COPD patients: a population database analysis. *Respir Med* 2012; 106: 1124–1133.
30. Keatings VM, Collins PD, Scott DM, *et al.* Differences in interleukin-8 and tumor necrosis factor- α in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am J Respir Crit Care Med* 1996; 153: 530–534.
31. Keatings VM, Barnes PJ. Granulocyte activation markers in induced sputum: comparison between chronic obstructive pulmonary disease, asthma and normal subjects. *Am J Respir Crit Care Med* 1997; 155: 449–453.
32. Biernacki WA, Kharitonov SA, Barnes PJ. Increased leukotriene B4 and 8-isoprostane in exhaled breath condensate of patients with exacerbations of COPD. *Thorax* 2003; 58: 294–298.
33. Aaron SD, Angel JB, Lunau M, *et al.* Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 349–355.
34. Van Pottelberge GR, Bracke KR, Demedts IK, *et al.* Selective accumulation of langerhans-type dendritic cells in small airways of patients with COPD. *Respir Res* 2010; 11: 35.
35. Di Stefano A, Caramori G, Capelli A, *et al.* STAT4 activation in smokers and patients with chronic obstructive pulmonary disease. *Eur Respir J* 2004; 24: 78–85.
36. Di Stefano A, Caramori G, Gnemmi I, *et al.* T helper type 17-related cytokine expression is increased in the bronchial mucosa of stable chronic obstructive pulmonary disease patients. *Clin Exp Immunol* 2009; 157: 316–324.
37. Pridgeon C, Bugeon L, Donnelly L, *et al.* Regulation of IL-17 in chronic inflammation in the human lung. *Clin Sci (Lond)* 2011; 120: 515–524.
38. Costa C, Rufino R, Traves SL, *et al.* CXCR3 and CCR5 chemokines in the induced sputum from patients with COPD. *Chest* 2008; 133: 26–33.
39. Saetta M, Mariani M, Panina-Bordignon P, *et al.* Increased expression of the chemokine receptor CXCR3 and its ligand CXCL10 in peripheral airways of smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 165: 1404–1409.
40. Kirkham PA, Caramori G, Casolari P, *et al.* Oxidative stress-induced antibodies to carbonyl-modified protein correlate with severity of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011; 184: 796–802.
41. Karayama M, Inui N, Suda T, *et al.* Antiendothelial cell antibodies in patients with COPD. *Chest* 2010; 138: 1303–1308.
42. Majo J, Ghezzi H, Cosio MG. Lymphocyte population and apoptosis in the lungs of smokers and their relation to emphysema. *Eur Respir J* 2001; 17: 946–953.
43. Lambers C, Hacker S, Posch M, *et al.* T cell senescence and contraction of T cell repertoire diversity in patients with chronic obstructive pulmonary disease. *Clin Exp Immunol* 2009; 155: 466–475.
44. Hodge G, Mukaro V, Reynolds PN, *et al.* Role of increased CD8/CD28^{null} T cells and alternative co-stimulatory molecules in chronic obstructive pulmonary disease. *Clin Exp Immunol* 2011; 166: 94–102.
45. Montuschi P, Kharitonov SA, Ciabattini G, *et al.* Exhaled leukotrienes and prostaglandins in COPD. *Thorax* 2003; 58: 585–588.

46. Beeh KM, Kornmann O, Buhl R, *et al.* Neutrophil chemotactic activity of sputum from patients with COPD: role of interleukin 8 and leukotriene B₄. *Chest* 2003; 123: 1240–1247.
47. Yokomizo T. Leukotriene B₄ receptors: novel roles in immunological reactions. *Adv Enzyme Regul* 2011; 51: 59–64.
48. Barnes PJ. The cytokine network in COPD. *Am J Respir Cell Mol Biol* 2009; 41: 631–638.
49. Birrell MA, Eltom S. The role of the NLRP3 inflammasome in the pathogenesis of airway disease. *Pharmacol Ther* 2011; 130: 364–370.
50. Doe C, Bafadhel M, Siddiqui S, *et al.* Expression of the T helper 17-associated cytokines IL-17A and IL-17F in asthma and COPD. *Chest* 2010; 138: 1140–1147.
51. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med* 2010; 363: 2233–2247.
52. O'Reilly P, Jackson PL, Noerager B, *et al.* N-alpha-PGP and PGP, potential biomarkers and therapeutic targets for COPD. *Respir Res* 2009; 10: 38.
53. Bowler RP, Barnes PJ, Crapo JD. The role of oxidative stress in chronic obstructive pulmonary disease. *J COPD* 2004; 2: 255–277.
54. Montuschi P, Barnes PJ, Roberts LJ. Isoprostanes: markers and mediators of oxidative stress. *FASEB J* 2004; 18: 1791–1800.
55. Osoata GO, Hanazawa T, Brindicci C, *et al.* Peroxynitrite elevation in exhaled breath condensate of COPD and its inhibition by fudosteine. *Chest* 2009; 135: 1513–1520.
56. Brindicci C, Kharitonov SA, Ito M, *et al.* Nitric oxide synthase isoenzyme expression and activity in peripheral lungs of COPD patients. *Am J Respir Crit Care Med* 2010; 181: 21–30.
57. Malhotra D, Thimmulappa R, Navas-Acien A, *et al.* Decline in NRF2 regulated antioxidants in COPD lungs due to loss of its positive regulator DJ-1. *Am J Respir Crit Care Med* 2008; 178: 592–604.
58. Malhotra D, Thimmulappa RK, Mercado N, *et al.* Denitrosylation of HDAC2 by targeting Nrf2 restores glucocorticosteroid sensitivity in macrophages from COPD patients. *J Clin Invest* 2011; 121: 4289–4302.
59. Tomita K, Barnes PJ, Adcock IM. The effect of oxidative stress on histone acetylation and IL-8 release. *Biochem Biophys Res Comm* 2003; 301: 572–577.
60. Nakamaru Y, Vuppusetty C, Wada H, *et al.* A protein deacetylase SIRT1 is a negative regulator of metalloproteinase-9. *FASEB J* 2009; 23: 2810–2819.
61. Adcock IM, Caramori G, Barnes PJ. Chronic obstructive pulmonary disease and lung cancer: new molecular insights. *Respiration* 2011; 81: 265–284.
62. Rahman I, Morrison D, Donaldson K, *et al.* Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med* 1996; 154: 1055–1060.
63. Groenewegen KH, Postma DS, Hop WC, *et al.* Increased systemic inflammation is a risk factor for COPD exacerbations. *Chest* 2008; 133: 350–357.
64. Gan WQ, Man SF, Senthilselvan A, *et al.* Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574–580.
65. van Eeden SF, Sin DD. Chronic obstructive pulmonary disease: a chronic systemic inflammatory disease. *Respiration* 2008; 75: 224–238.
66. Thomsen M, Dahl M, Lange P, *et al.* Inflammatory biomarkers and comorbidities in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 982–988.
67. Agustí A, Edwards LD, Rennard SI, *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7: e37483.
68. Hurst JR, Donaldson GC, Perea WR, *et al.* Utility of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 174: 867–874.
69. Dahl M, Vestbo J, Lange P, *et al.* C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 250–255.
70. de Torres JP, Pinto-Plata V, Casanova C, *et al.* C-reactive protein levels and survival in patients with moderate to very severe COPD. *Chest* 2008; 133: 1336–1343.
71. Fogarty AW, Jones S, Britton JR, *et al.* Systemic inflammation and decline in lung function in a general population: a prospective study. *Thorax* 2007; 62: 515–520.
72. Perera WR, Hurst JR, Wilkinson TM, *et al.* Inflammatory changes, recovery and recurrence at COPD exacerbation. *Eur Respir J* 2007; 29: 527–534.
73. Donaldson GC, Seemungal TA, Patel IS, *et al.* Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest* 2005; 128: 1995–2004.
74. Dahl M, Tybjaerg-Hansen A, Vestbo J, *et al.* Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1008–1011.
75. Bozinovski S, Hutchinson A, Thompson M, *et al.* Serum amyloid A is a biomarker of acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 269–278.
76. Bozinovski S, Uddin M, Vlahos R, *et al.* Serum amyloid A opposes lipoxin A₄ to mediate glucocorticoid refractory lung inflammation in chronic obstructive pulmonary disease. *Proc Natl Acad Sci USA* 2012; 109: 935–940.
77. Cheng N, He R, Tian J, *et al.* Cutting edge: TLR2 is a functional receptor for acute-phase serum amyloid A. *J Immunol* 2008; 181: 22–26.

78. Sin DD, Leung R, Gan WQ, *et al.* Circulating surfactant protein D as a potential lung-specific biomarker of health outcomes in COPD: a pilot study. *BMC Pulm Med* 2007; 7: 13.
79. Winkler C, Atochina-Vasserman EN, Holz O, *et al.* Comprehensive characterisation of pulmonary and serum surfactant protein D in COPD. *Respir Res* 2011; 12: 29.
80. Bhowmik A, Seemungal TA, Sapsford RJ, *et al.* Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000; 55: 114–120.
81. Yende S, Waterer GW, Tolley EA, *et al.* Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. *Thorax* 2006; 61: 10–16.
82. Janssen SP, Gayan-Ramirez G, Van den BA, *et al.* Interleukin-6 causes myocardial failure and skeletal muscle atrophy in rats. *Circulation* 2005; 111: 996–1005.
83. Broekhuizen R, Grimble RF, Howell WM, *et al.* Pulmonary cachexia, systemic inflammatory profile, and the interleukin 1 β -511 single nucleotide polymorphism. *Am J Clin Nutr* 2005; 82: 1059–1064.
84. de Godoy I, Donahoe M, Calhoun WJ, *et al.* Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. *Am J Respir Crit Care Med* 1996; 153: 633–637.
85. Takabatake N, Nakamura H, Abe S, *et al.* The relationship between chronic hypoxemia and activation of the tumor necrosis factor- α system in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1179–1184.
86. Tracey KJ, Wei H, Manogue KR, *et al.* Cachectin/tumor necrosis factor induces cachexia, anemia, and inflammation. *J Exp Med* 1988; 167: 1211–1227.
87. Spruit MA, Gosselink R, Troosters T, *et al.* Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003; 58: 752–756.
88. Weiss ST, Segal MR, Sparrow D, *et al.* Relation of FEV₁ and peripheral blood leukocyte count to total mortality. The Normative Aging Study. *Am J Epidemiol* 1995; 142: 493–498.
89. Grimm RH Jr, Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. *JAMA* 1985; 254: 1932–1937.
90. Sparrow D, Glynn RJ, Cohen M, *et al.* The relationship of the peripheral leukocyte count and cigarette smoking to pulmonary function among adult men. *Chest* 1984; 86: 383–386.
91. Macnee W, Wiggs B, Belzberg AS, *et al.* The effect of cigarette smoking on neutrophil kinetics in human lungs. *N Engl J Med* 1989; 321: 924–928.
92. Suwa T, Hogg JC, Quinlan KB, *et al.* The effect of interleukin-6 on L-selectin levels on polymorphonuclear leukocytes. *Am J Physiol Heart Circ Physiol* 2002; 283: H879–H884.
93. van Eeden SF, Lawrence E, Sato Y, *et al.* Neutrophils released from the bone marrow by granulocyte colony-stimulating factor sequester in lung microvessels but are slow to migrate. *Eur Respir J* 2000; 15: 1079–1086.
94. Noguera A, Batle S, Miralles C, *et al.* Enhanced neutrophil response in chronic obstructive pulmonary disease. *Thorax* 2001; 56: 432–437.
95. Noguera A, Sala E, Pons AR, *et al.* Expression of adhesion molecules during apoptosis of circulating neutrophils in COPD. *Chest* 2004; 125: 1837–1842.
96. Pons J, Sauleda J, Ferrer JM, *et al.* Blunted $\gamma\delta$ T-lymphocyte response in chronic obstructive pulmonary disease. *Eur Respir J* 2005; 25: 441–446.
97. Fairclough L, Urbanowicz RA, Corne J, *et al.* Killer cells in chronic obstructive pulmonary disease. *Clin Sci (Lond)* 2008; 114: 533–541.
98. Urbanowicz RA, Lamb JR, Todd I, *et al.* Altered effector function of peripheral cytotoxic cells in COPD. *Respir Res* 2009; 10: 53.
99. Chi SY, Ban HJ, Kwon YS, *et al.* Invariant natural killer T cells in chronic obstructive pulmonary disease. *Respirology* 2012; 17: 486–492.
100. Steiner S, Pfutzner A, Wilson BR, *et al.* Technosphere/insulin – proof of concept study with a new insulin formulation for pulmonary delivery. *Exp Clin Endocrinol Diabetes* 2002; 110: 17–21.
101. van Eeden SF, Tan WC, Suwa T, *et al.* Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM₁₀). *Am J Respir Crit Care Med* 2001; 164: 826–830.
102. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of “overspill” of inflammatory mediators from the lungs? Review of the evidence. *Thorax* 2010; 65: 930–936.
103. de Torres JP, Marin JM, Casanova C, *et al.* Lung cancer in patients with chronic obstructive pulmonary disease—incidence and predicting factors. *Am J Respir Crit Care Med* 2011; 184: 913–919.
104. Young RP, Hopkins RJ, Christmas T, *et al.* COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. *Eur Respir J* 2009; 34: 380–386.
105. Caramori G, Adcock IM, Casolari P, *et al.* Unbalanced oxidant-induced DNA damage and repair in COPD: a link towards lung cancer. *Thorax* 2011; 66: 521–527.
106. Barnes PJ. Development of new drugs for COPD. *Curr Med Chem* 2012; *In press*.
107. Wouters EF, Bredenbroeker D, Teichmann P, *et al.* Effect of the phosphodiesterase 4 inhibitor roflumilast on glucose metabolism in patients with treatment-naïve, newly diagnosed type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2012; 97: E1720–E1725.

Chapter 3

Assessment of cardiovascular comorbidity



John D. Maclay* and William MacNee[#]

SUMMARY: Cardiovascular disease is common in COPD patients and is associated with poor clinical outcome. These conditions may share common pathogenic mechanisms. Cardiovascular disease should be actively sought, assessed and treated in COPD patients; this may improve clinical outcome in these patients. Prospective studies are needed to determine whether the use of cardiovascular drugs is a useful treatment in COPD patients.

KEYWORDS: Cardiovascular disease, COPD, coronary artery disease, vascular function

*Gartnavel General Hospital, Glasgow, and

[#]The University of Edinburgh, The Queen's Medical Research Institute, Edinburgh, UK.

Correspondence: W. MacNee, UoE/ MRC Centre for Inflammation Research, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK.
Email: w.macnee@ed.ac.uk

Eur Respir Monogr 2013; 59: 28–49.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011312
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

COPD and cardiovascular disease, specifically coronary artery disease (CAD), are common conditions whose prevalence is likely to increase with ageing of the population.

Although cardiovascular disease and COPD were previously considered to be two distinct conditions linked by common aetiological factors, there is now considerable evidence, from epidemiological, clinical and experimental studies, that there is a more complex relationship between COPD and CAD than the simple coexistence of both conditions and that these conditions may have common pathogenic mechanisms.

Population-based studies indicate that cardiovascular mortality accounts for 20–30% of deaths in patients with COPD and that the risk of cardiovascular mortality is twice as great in COPD patients [1, 2]. Reduced lung function, measured by a decrease in forced expiratory volume in 1 second (FEV₁), is associated with all-cause mortality, cardiac mortality, myocardial infarction (MI) and arrhythmia [3–6], and FEV₁ is a better predictor of cardiovascular mortality than cholesterol [7].

In this chapter, we will provide a review of the epidemiology of COPD and CAD, the mechanisms that link these conditions, and the assessment and treatment of CAD in COPD patients.

Increased risk of cardiovascular disease in COPD

Coronary artery disease

Cigarette smoking is a leading risk factor for both COPD and CAD [7–9]. Many studies, in various cohorts, have shown that FEV₁ is a significant risk factor for cardiovascular morbidity and mortality independent of smoking (fig. 1) [10–12]. Furthermore, the relationship between FEV₁

and mortality for CAD and stroke is present even in lifelong nonsmokers [7]. A cardiovascular cause of death is common in COPD patients and accounts for between 12% and 37% of deaths in various studies [13], and seems to be related to the severity of the airflow limitation, with a higher percentage of deaths in subjects with mild-to-moderate airflow limitation [14].

Cardiovascular events are also common in COPD patients. They were the leading cause of hospitalisation in smokers with mild-to-moderate COPD in the Lung Health Study, accounting for almost 50% of hospital admissions [15]. SORIANO *et al.* [16] described the prevalence of cardiovascular comorbidities in newly diagnosed patients with COPD from a large general practice

research database in the UK; angina and MI occurred in >1% of patients within the first year after diagnosis of COPD. In a large retrospective study of a cohort of COPD patients, angina was reported in 6.6% and acute MI in 2.3% of patients [17]. The Third National Health and Nutritional Examination Survey demonstrated that patients with moderate or severe airflow limitation had more evidence of ischaemic changes on their ECG than those without airflow limitation [18]. In a large UK database of primary care medical records, comprising 1,204,110 patients aged >35 years, 29,870 patients were identified with COPD and these patients were five times more likely to have cardiovascular disease compared with those without COPD [19]. Follow-up of these patients showed that the incidence of MI was greater in COPD patients than those without COPD after adjusting for important confounding factors, such as age and smoking. In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study, “heart trouble” was reported in 26% of 2,164 COPD patients, compared with 11% of 337 smoking controls, and MI was reported in 9% *versus* 3% [20].

In two large population-based studies (Atherosclerosis Risk in Communities (ARIC) and the Cardiovascular Health Study (CHS)) comprising 20,296 patients over the age of 44 years, the prevalence of cardiovascular disease in COPD patients was between 20% and 22%, compared with 9% of subjects without COPD [14, 21]. A large longitudinal Canadian health database study found that COPD patients had a higher risk ratio for angina (OR 2.02) and MI (OR 1.99) compared with matched controls after adjustment for important known cardiovascular risk factors [17].

The relationship between the severity of the airflow limitation and cardiovascular risk varies in the literature. In the ECLIPSE study, there was no relationship between severity of airflow limitation or the decline in FEV₁ in the COPD cohort and the presence of cardiovascular comorbidities [20], whereas in the ARIC population study, the incidence of cardiovascular events over a 15-year follow-up period was more frequent in subjects with a lower FEV₁ regardless of smoking status or the presence of cardiovascular disease at baseline [22]. CURKENDALL *et al.* [23] stratified COPD patients in terms of clinical indicators of severity and found that the most severe quintile of patients had higher cardiovascular morbidity and mortality (OR 1.63) than the least severe quintile.

Several population-based studies have reported a relationship between FEV₁ and cardiovascular mortality (table 1) [7, 11, 24, 25]. These studies show some heterogeneity but the results do indicate that reduced FEV₁ independent of established risk factors, such as cigarette smoking, total

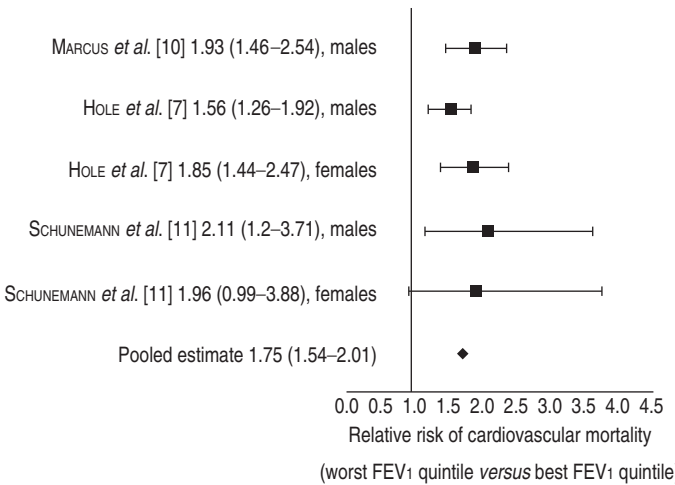


Figure 1. Meta-analysis of studies that reported relative risks with 95% confidence intervals (represented by the whiskers) of cardiovascular mortality based on forced expiratory volume in 1 second (FEV₁) quintiles (worst FEV₁ *versus* best FEV₁ quintile). Reproduced and modified from [12] with permission from the publisher.

Table 1. Baseline characteristics of studies reported since 1990 and the association between forced expiratory volume in 1 second (FEV₁) and cardiovascular mortality

First author [ref.]	Study population	Subjects n	Age years	Males %	Mean FEV ₁	Current smokers %	FEV ₁ categorisation	Follow-up years	RR of cardiovascular mortality (95% CI)	Adjusted factors
HOLE [7]	Renfrew and Paisley, UK	15411	45–64	46	2.83 L [#] 1.99 L [*]	36	Quintiles ≤73–75 versus ≥108–113% pred	15	1.56 (1.26–1.92) 1.88 (1.44–2.47)	Age, smoking status and history, blood pressure, serum cholesterol, BMI, social class
SCHUNEMANN [11]	Buffalo and Erie County, NY, USA	1195	47	46	2.8 L	58	Quintiles <80 versus ≥109–114% pred	29	2.11 (1.20–3.71) [#] 1.96 (0.99–3.88) [*]	Age, education, smoking status, blood pressure, BMI
HOSPERS [24]	Vlaagtwedde-Vlaardingen, the Netherlands	5382	36	54	98% pred	55	<80 versus ≥100% pred	~25	1.82 (1.42–2.34)	Sex, age, smoking status, BMI
KNUIMAN [25]	Busselton, Australia	4277	49	49	95% pred [#] /100% pred [*]	45 [#] /24 [*]	10% decrease in FEV ₁ % pred	20–26	1.10 (1.03–1.18) [#] 1.07 (1.00–1.24) [*]	Age, smoking status and history, symptoms, coronary heart disease, cardiovascular risk factors

RR: relative risk; % pred: % predicted; BMI: body mass index. [#]: males; ^{*}: females. Reproduced and modified from [26] with permission from the publisher.

cholesterol or hypertension, is an important risk factor for cardiovascular mortality. In general, when the lowest quintile of FEV₁ is compared with the highest quintile, risk of cardiovascular mortality increases by approximately 75% in both males and females.

A greater decline in FEV₁ is also associated with increased cardiovascular risk. In the study of Malmö males born in 1914, the cardiovascular event rate among smokers in the high, middle and low tertiles of decline in FEV₁ was 56.0, 41.0 and 22.7 events per 1,000 person-years ($p=0.01$) [27]. In the Baltimore Longitudinal Study of Aging, patients with the greatest decline in FEV₁ over a 16-year follow-up period were three to five times more likely to die from a cardiac cause than those with the lowest decline in FEV₁, after adjusting for major confounding factors [28]. Even among lifetime nonsmokers, an accelerated decline in FEV₁ was associated with a five- to 10-fold increase in risk of cardiac death, suggesting that the relationship between changes in FEV₁ and cardiovascular events is independent of the effects of smoking.

Studies have also shown that individuals with a reduced FEV₁ are at increased risk of atherosclerosis. In a cross-sectional study of 94 healthy middle-aged males considered to be free of CAD, the FEV₁ was related to the pulse wave velocity (PWV), a measurement of central arterial stiffness and atherosclerosis, which was independent of other well-established risk factors for atherosclerosis (fig. 2) [29]. For every 93-mL decrement in FEV₁, the PWV increased by 2.5 m·s⁻¹ in the subjects in this study [29]. Smokers with airflow limitation have also been shown to have evidence of subclinical atherosclerosis as measured by carotid intimal medial thickness (CIMT) (fig. 3) [30]. In addition, increased PWV has been shown to be associated with worsening airflow limitation and with the extent of emphysema (fig. 4) [31].

The prevalence of COPD is also high among patients with CAD, largely from studies in patients with CAD hospitalised for acute coronary syndrome [32, 33] or in patients in clinical trials [34]. The reported prevalence of COPD among patients with MI vary between 16% [35] and 7% [36], which may reflect differences in the patients enrolled in these studies. However, in a more recent study, which included all individuals with their first MI, the prevalence of COPD was 12% [37]. Airflow limitation compatible with COPD was reported in 33.6% of patients with CAD attending a tertiary referral outpatient clinic, compared with a prevalence of 17% in control subjects [38]. Moreover, many patients in this study with moderate-to-severe airflow limitation had never been diagnosed with COPD, suggesting that the relationship between COPD and cardiovascular disease is under-recognised.

The presence of CAD has important adverse effects and prognostic implications in patients with COPD. In a number of studies, the proportion of deaths attributed to cardiac disease in patients with COPD varied between 12% and 50% depending on the population studied (table 2) [48]. In the pooled analysis of two large population-based epidemiological studies (ARIC and CHS), the presence of cardiovascular disease conferred a significantly higher risk of hospital admission and mortality within 5 years [8]. The Kaiser Permanente Medical Care Programme, in Northern California (USA), matched more than 45,000 COPD patients with an equal number of controls without COPD, and found that mortality for all cardiovascular diseases was higher in COPD patients than among control subjects [49]. In the Towards a Revolution in COPD Health (TORCH) study, 26% of COPD patients died from cardiovascular disease [41].

The course of COPD is often characterised by exacerbations, which are associated with increased mortality, not only during the acute event but also over the long term. The presence of cardiovascular disease may prolong the course of exacerbations [50]. In addition, exacerbations of COPD are associated with acute cardiovascular events. In 25,857 patients with COPD from the Health Improvement Network database, the risk of MI 1–5 days after exacerbation increased two- to three-fold [51]. Retrospective studies have shown that concentrations of troponin: are raised during exacerbations of COPD; reflect the severity of the exacerbation even in the absence of a diagnosis of MI [52]; and are associated with increased risk of death after hospital discharge [53]. Prospective studies have confirmed that an elevated serum level of N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T in patients hospitalised with acute severe exacerbations of COPD is associated both with increased 30-day and long-term mortality, independent of other known prognostic factors [54, 55]. In a further prospective study, McALLISTER *et al.* [56] showed a prevalence of MI of 8.3% in a cohort of 242 patients with an exacerbation of COPD.

The presence of heart disease (although not specifically ischaemic heart disease) is associated with poor outcome in COPD patients. In a large Spanish cohort of COPD patients, the presence of heart disease was associated with less physical activity and poor health-related quality of life compared with those patients without comorbid heart disease [57]. Those patients with COPD and heart disease consumed significantly more resources than those without comorbid heart disease, as shown by an increase in primary and secondary care consultations, visits to emergency departments, hospitalisations, and duration of hospital admissions with associated

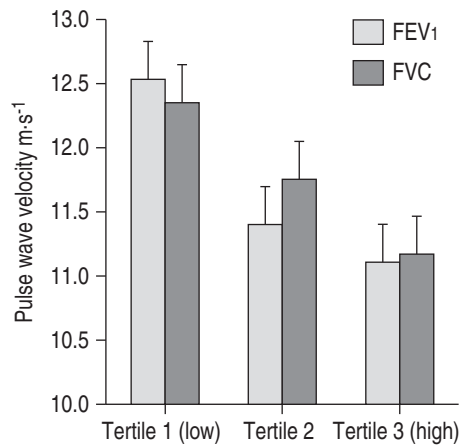


Figure 2. Pulse wave velocity, adjusted for age, height, weight, smoking habit, hypercholesterolaemia, diabetes and hypertension by tertiles of forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC). Data are presented as mean $\pm$ SEM. Ranges for tertiles: FEV₁ 1,530–3,010, 3,020–3,640 and 3,650–5,190 mL; FVC 2,060–3,650, 3,660–4,380 and 4,390–6,270 mL. $p < 0.05$ for linear trend for FEV₁ and FVC. Reproduced and modified from [29] with permission from the publisher.

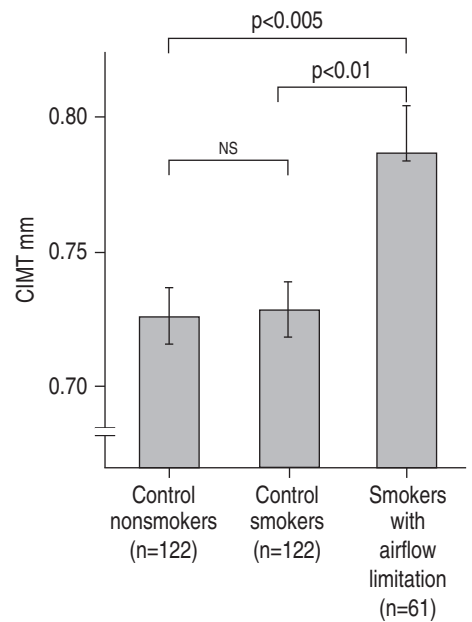


Figure 3. Airflow limitation in smokers is associated with subclinical atherosclerosis as measured by carotid intimal medial thickness (CIMT). Data are presented as mean (95% CI). Reproduced and modified from [30] with permission from the publisher.

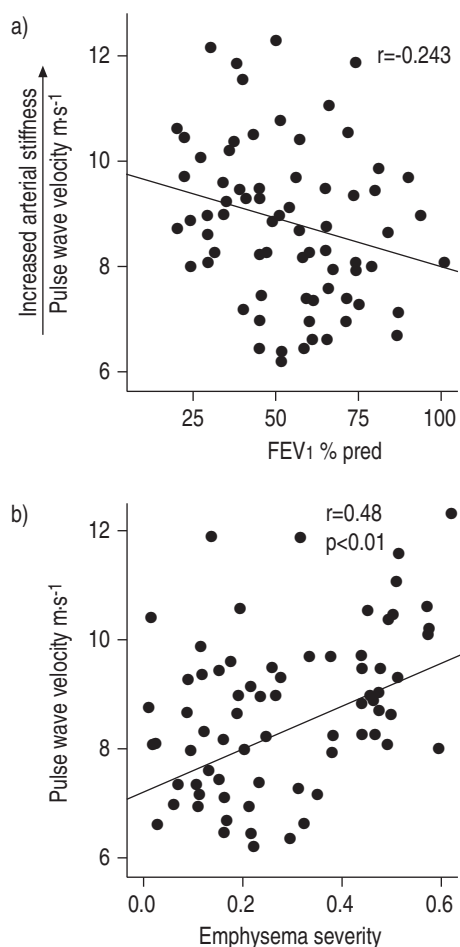


Figure 4. The relationship between pulse wave velocity as a measure of arterial stiffness and a) forced expiratory volume in 1 second (FEV₁) % predicted and b) computed tomography emphysema severity as measured by the pixel index -910 Hounsfield units. Reproduced and modified from [31] with permission from the publisher.

community-based populations [66]. In a US cohort of adults aged 45–64 years followed for an average of 15 years, the hazard ratio (HR) for the incidence of heart failure increased with decreased quartiles of FEV₁, even after adjustment for age, sex, heart disease, smoking and other cardiovascular risk factors [67]. Thus, from these studies, it appears that airflow limitation itself is a major risk factor of heart failure. Furthermore, airflow limitation can also be a consequence of heart failure [68].

Hypertension

Hypertension is reported in 40–60% of COPD patients [8, 17]. In the ARIC and CHS population-based cohorts, the prevalence of hypertension was 34% in normal subjects but 40% in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I COPD patients, 44% in GOLD stage II and 51% in GOLD stage III and IV COPD patients [8], with an odds ratio of having hypertension of 1.4 in GOLD stage II and 1.6 in GOLD stage III and IV patients compared with normal subjects. The presence of hypertension in COPD patients increased the risk of hospitalisation within 5 years as well as the risk of mortality [8]. The links between COPD and

increased healthcare costs [57]. In the ECLIPSE COPD cohort, patients with cardiovascular disease and COPD were characterised by an increased body mass index (BMI), worsening symptoms, poor exercise tolerance and high systemic inflammation [58], results that were replicated in a further COPD cohort study [50].

Heart failure

Heart failure secondary to ischaemic heart disease or hypertension is generally overlooked or underestimated in COPD patients [59]. In a primary care setting, 20.5% of patients with a diagnosis of COPD had previously unrecognised heart failure. The overall prevalence of heart failure in the cohort of COPD patients with moderate-to-severe airflow limitation in the ECLIPSE study was 7% [20], whereas in a cohort of outpatients with heart failure, 39% were found to have COPD, which was associated with a shorter time to hospital admission or death [60]. The prevalence of COPD in heart failure patients and their survival is similar to that seen in those with normal or abnormal left ventricular ejection fraction [61].

COPD is also a predictor of mortality in heart failure [62]. In a large acute heart failure registry from the USA, patients with heart failure with reduced left ventricular ejection fraction, who had a diagnosis of COPD, had a longer duration of hospitalisation, reduced use of heart failure therapies and higher in-patient mortality compared to patients with heart failure without COPD [63]. In newly diagnosed hospitalised heart failure patients, those with COPD had a 5-year all-cause mortality of 71%, compared with 31% mortality in heart failure patients without COPD [64]. The FEV₁ % predicted was itself an independent predictor of all-cause mortality in patients admitted with heart failure [65]. These studies are consistent with other recently published longitudinal studies in

Table 2. Proportion of deaths attributed to cardiac disease in patients with COPD

First author [ref.]	Year	Subjects n	Follow-up years	Age years	All cardiac causes %
ANTHONISEN [15] [#]	1994	5887	5	48	25
ANTHONISEN [39] [#]	2005	5887	14.5	48	22
CALVERLEY [40] [#]	2007	6112	3	65	16
MCGARVEY [41]	2007	6184	3	65	27
MCGARVEY [42] [#]	2011	5992	4	65	23
VILKMAN [43]	1997	2727	8.5	50–54	38 [†] 26 ⁺
ENGSTRÖM [44]	2001	200	14	68	50
GARCIA-AYMERICH [45]	2003	340	1.1	69	12
CELLI [46]	2004	625	2.3	64–67	14
STAVEM [47]	2005	405	26	50	45
CURKENDALL [17]	2006	7575	4	>65	30

Data are presented as means, unless otherwise stated. [#]: randomised controlled trial; [†]: males; ⁺: females. Reproduced and modified from [48] with permission from the publisher.

hypertension are not well described; however, accelerated ageing with degradation of elastin and increased deposition of collagen resulting in increased arterial stiffness may play a role. Arterial stiffness has been shown to be increased in COPD patients, and is related to FEV₁ and emphysema [31]. Recent studies suggest that increased arterial stiffness in COPD may be related to increased elastic connective tissue loss [69].

Arrhythmias

Arrhythmias have an estimated prevalence of 12–14% in COPD patients [16, 70]. The majority of arrhythmias in COPD are atrial fibrillation, which is more common with increasing severity of airflow limitation [71] and in exacerbations of COPD, and is likely to reflect the presence of underlying ischaemic heart disease.

Stroke

In a large survey of the primary care records of 1,204,100 members of the general population aged ≥35 years, the prevalence of stroke was 9.9% in those with COPD, compared with a prevalence of 3.2% in the rest of the population [19]. In the follow-up study, COPD was associated with a 2.8-fold increase in the incidence of acute stroke [19]. In another study, conducted as a telephone survey in the USA, 14% of COPD patients reported a previous cerebrovascular event [21]. In the first 7 weeks following an exacerbation of COPD, there is a 1.3-fold increased risk of stroke [51].

The mechanisms that link COPD with stroke are similar to those for CAD described later in this chapter. Studies have shown that carotid arterial plaque burden is increased in COPD patients compared with matched healthy subjects, which is related to the severity of the airflow limitation [30, 72, 73]. In addition, the use of high-resolution magnetic resonance imaging to characterise carotid plaques has shown that patients with COPD were more likely than subjects without COPD to harbour vulnerable plaques characterised by increased lipid content [72], which had a greater tendency of rupture leading to stroke.

Mechanisms of increased cardiovascular risk in COPD

Traditional risk factors

The large population-based studies described earlier suggest that FEV₁ and COPD are independent risk factors for cardiovascular disease. It is, however, difficult to adjust statistically for traditional risk factors like hypertension and more difficult still to adjust for cigarette smoke exposure, a risk

factor for both COPD and cardiovascular disease. What is clear is that patients with COPD have increased susceptibility to cigarette smoke compared with other smokers who do not develop the disease. Although this has previously been described in relation to the pulmonary manifestations of this condition, it is reasonable to assume that the same may be true for its effects on the vasculature. IWAMOTO *et al.* [30] described an increase in CIMT in COPD patients in comparison with matched smoking controls. CIMT is an indirect measure of plaque burden, suggesting that susceptible smokers who develop COPD are prone to develop subclinical atherosclerosis.

An atherogenic lipid pattern is unlikely to be a major cause of the increased vascular risk in COPD since lipid levels in COPD patients are similar to those in healthy subjects [74]. Hypertension, which is a risk factor for CAD, is a common comorbidity in COPD and is reported to occur in 40–60% of COPD patients [8, 17].

COPD is associated with an increased prevalence of diabetes and the metabolic syndrome, which are risk factors for cardiovascular disease. In the Framingham Heart Study, WALTER *et al.* [75] reported an increased prevalence of diabetes in subjects with lower than predicted lung function. INCALZI *et al.* [76] found a prevalence of diabetes of 14% in patients admitted with COPD. In a large population-based study reviewing hospital discharges, diabetes was a comorbidity in 11% of discharges where COPD was the primary diagnosis [77]. Type 2 diabetes mellitus and impaired glucose tolerance are recognised complications of systemic corticosteroid use. Thus, patients with more severe disease, who are prone to increased frequency and severity of exacerbations, may be more prone to developing diabetes as a result of corticosteroid treatment. In addition, chronic elevation of inflammatory mediators raised in COPD, including interleukin (IL)-6, tumour necrosis factor (TNF)- α and C-reactive protein (CRP), is associated with development of diabetes and insulin resistance [78]. This has been explored in a small case–control study that linked the increased prevalence of insulin resistance found in COPD patients compared with healthy subjects to levels of circulating inflammatory markers [79]. MANNINO *et al.* [8] reported an increased prevalence of diabetes and hypertension in patients with COPD in comparison with healthy individuals and especially in subjects with moderate-to-severe airflow obstruction.

Physical inactivity is an independent risk factor for many chronic diseases, including coronary heart disease, obesity, stroke and type 2 diabetes [80–82]. Both of these factors are associated with low-grade systemic inflammation, which also occurs in COPD patients and may contribute to the increase in cardiovascular disease in COPD patients.

Novel risk factors

There is now evidence that, in addition to the role of traditional risk factors, more novel, mechanistic risk factors are known to contribute to the pathogenesis of cardiovascular disease. These novel mechanisms of cardiovascular disease are also described in COPD, and may be the link between the increased risk of cardiovascular disease and COPD.

Systemic inflammation

The formation of the atherosclerotic plaque was thought to be the primary process in the pathogenesis of cardiovascular disease: endothelial denudation and proliferation of smooth muscle cells formed an atheroma with deposition of lipid in its core. However, a proportion of patients who die of sudden cardiac events have no prior symptoms or history of CAD, which is likely to result from rupture of occult atherosclerotic plaques [83].

Subsequent studies have shown that specific inflammatory cells and their pathways play key roles in the formation of atherosclerotic plaques, plaque rupture and atherothrombosis that lead to cardiac events [84]. Recruitment of monocytes and platelets, activated by release of chemokines following endothelial damage, express cell surface receptors allowing formation of platelet–monocyte aggregates that attach to the denuded surface. Monocytes transmigrate into the sub-intimal space and differentiate into macrophages that ingest cholesterol lipoproteins to form the lipid-rich core of atheromatous plaques. Smooth muscle cells are recruited by T-lymphocytes and

macrophages to form a fibrous cap, along with extracellular matrix. The thickness of the fibrous cap determines the vulnerability of the plaque to rupture, which can lead to atherothrombosis, release of subendothelial matrix elements, activation of platelets and thrombosis formation, causing a cardiac event [85]. Macrophages accumulate in the shoulder of vulnerable plaques, the site at which most plaques rupture [86]. Subsequent secretion of matrix metalloproteinases can damage the extracellular matrix, weakening the cap.

While these local inflammatory processes lead to atheroma formation and play a crucial role in the development of plaque rupture and, therefore, acute coronary syndromes, circulating markers of inflammation are now known to predict cardiac events. CRP, an acute-phase reactant produced in response to acute injury, infection or inflammation, is a strong predictor of future cardiac events. In two prospective studies of healthy males and females, baseline CRP predicted cardiovascular events, independent of traditional risk factors [87, 88]. CRP also predicts recurrent events in patients with known coronary disease. RIDKER *et al.* [89] investigated the use of statins in healthy participants with normal low-density lipoprotein-cholesterol levels and found that statins reduced the incidence of major cardiovascular events in comparison to placebo. After treatment, the statin group did have significantly lower CRP levels than the placebo group.

Systemic inflammation is an extrapulmonary manifestation of COPD. The source of this inflammation is currently unclear. However, markers of inflammation, particularly CRP, are elevated in patients with COPD in comparison with controls [90]. Moreover, increased levels are associated with both disease severity and mortality [91, 92]. A recent study has shown that sustained elevation of systemic inflammatory markers occurred only in a proportion of patients (16%). However, those patients with sustained systemic inflammation had more cardiovascular disease and a six-fold greater mortality than those without systemic inflammation [58].

The mechanisms by which systemic inflammation plays a role in the pathogenesis of cardiovascular disease are complex. However, studies indicate the importance of inflammation in plaque initiation, development and rupture [93]. Vulnerable atherosclerotic plaques in the carotid arteries have recently been reported to occur more frequently in COPD patients than in age-matched control subjects [72].

Recent studies measuring cardiac biomarkers in acute exacerbations of COPD report increased mortality in those patients with raised troponin [54, 55]. However, raised troponin concentration was not associated with ECG changes [56]. It may be that a combination of systemic inflammation, oxidative stress and physiological stressors combine to cause subendocardial myocardial damage. Acute inflammation in the general population may also contribute to vascular events by causing rupture of vulnerable atherosclerotic plaques. Using a UK general practice database, risk of MI and stroke were shown to be highest in the first 3 days of developing a respiratory tract infection and urinary tract infection [94].

Vascular dysfunction

Dysfunction of large, medium and small vessels are risk factors for development of vascular events. Large vessel stiffness, affecting the aorta, is a physiological process that occurs with ageing. The aorta acts as the main buffer in response to the increase in pressure associated with systole [95]. Stiffening of the aorta results in increased pressure from the pulse wave, exposing distal vessels to higher shear stresses. In addition, there is increased load on the ventricles in systole and reduced coronary flow in diastole. Aortic PWV, a measure of arterial stiffness, predicts both cardiovascular events and mortality in healthy individuals [96]. Aortic PWV is increased in COPD in comparison to controls and is associated with both airflow obstruction and computed tomography (CT)-quantified emphysema severity after adjusting for important confounding factors [31]. Arterial stiffness may contribute to the increased cardiovascular risk in COPD.

Arterial stiffness is influenced by dysfunction of the three main structural components of the arterial wall: the extracellular matrix, vascular smooth muscle and endothelium. The endothelium has a role in vasodilatation, releasing vasoactive mediators including nitric oxide, prostacyclin and

endothelium hyperpolarising factor, causing relaxation of the vascular smooth muscle. It also releases tissue plasminogen activator (t-PA), the endogenous fibrinolytic mediator, and regulates local inflammation, releasing cytokines. The function of medium-sized conduit arteries has been assessed in COPD using flow-mediated dilatation (FMD) [97]. This technique, a noninvasive measure of endothelial function, employs ultrasound to assess the vasodilatation during reactive hyperaemia of the brachial artery following occlusion. Studies have shown that abnormalities of brachial artery FMD in COPD patients may have been, in part, due to abnormal endothelial function [98, 99]. Venous occlusion plethysmography measures blood flow across the forearm vascular bed, which is comprised predominantly of small arteriolar resistance vessels, and is another method of assessing endothelial function. Despite the presence of increased PWV in COPD patients compared with controls, there were no differences in endothelial vasomotor function or release of t-PA [100]. This may be due to vascular dysfunction affecting various sites differently in COPD or, alternatively, the abnormalities of vascular function detected at the brachial artery were due to other components of the arterial wall, such as the vascular smooth muscle or extracellular matrix.

Abnormal small vessel function is also associated with ageing and increased cardiovascular risk. In the Heart Outcomes Prevention Evaluation (HOPE) study, microalbuminuria predicted risk of cardiovascular events and death in individuals with and without diabetes [101]. This finding was replicated in patients with stable coronary disease in the Prevention of Events with an ACE inhibitor (PEACE) study [102]. CASANOVA *et al.* [103] measured urinary albumin/creatinine ratios and showed higher levels of microalbuminuria in COPD patients in comparison to smoking controls, suggesting damage to the renal microvasculature. Moreover, both VAN DIJK *et al.* [104] and, more recently, DODD *et al.* [105] have described white and grey matter changes along with cognitive dysfunction in COPD patients, which may be caused by small vessel disease.

Connective tissue degradation

In addition to the endothelium, the extracellular matrix in arterial walls contributes to large vessel compliance. Degradation of elastin in the presence of stiff collagen fibres is present as part of normal ageing and leads to arterial stiffness [106]. As well as elastin degradation in arterial walls, this phenomenon is also seen in the skin, causing wrinkling, and in the lungs, causing so-called “senile” emphysema.

Patients with COPD have evidence of both pulmonary and extrapulmonary elastin degradation. The lung destruction seen in emphysema is caused by elastin degradation [107]. Furthermore, patients with COPD have cutaneous elastin degradation as suggested by greater skin wrinkling than matched ex-smoking controls, which is related to CT-quantified emphysema [108]. Direct measurements of elastin degradation in the skin have been shown in COPD patients compared to matched controls [69] that correlated with the severity of emphysema and arterial stiffness. As mentioned earlier, arterial stiffness in COPD is associated with CT-quantified emphysema [31]. The hypothesis that COPD is a condition characterised by both pulmonary and systemic elastin degradation unites these findings.

The cause of extracellular matrix degradation is unclear. Protease/antiprotease imbalance is thought to contribute to the pathogenesis of COPD. Circulating monocytes release more matrix metalloproteinase (MMP)-9 in comparison to monocytes from healthy controls [109]. In a healthy population, circulating MMP-9 levels are associated with arterial stiffness, and polymorphisms in the *MMP9* gene predispose to arterial stiffness [110, 111]. MMP-2 is upregulated in the arteries of patients with chronic kidney disease, a condition associated with increased arterial stiffness, in comparison to matched donors [112]. MMP-9 mRNA expression has been shown to be increased in the skin of patients with COPD in comparison to matched controls, which was associated with skin elastin degradation [69].

Thus, degradation of the extracellular matrix in COPD both locally in the lungs and in the systemic vasculature may be explained in part by protease/antiprotease imbalance.

Oxidative stress

Increased pulmonary and systemic oxidative stress is present in COPD patients [113] and the latter has also been associated with ischaemic heart disease. Several of the traditional risk factors for CAD, including hypertension, hypercholesterolaemia, diabetes and smoking, are associated with increased production of oxygen free radicals from the vascular endothelium and smooth muscle cells. Reactive oxygen species (ROS) may be involved in the pathogenesis of atherosclerosis through a number of mechanisms: upregulation of cell adhesion molecules, proliferation of vascular smooth muscle, apoptosis of endothelium, lipid oxidation, activation of MMPs and altered vasomotor activity [114–117].

There is no direct evidence that increased oxidative stress in COPD increases cardiovascular risk. However, indirect evidence from studies of particulate air pollution have suggested that inhaled particulate matter may cause abnormal endothelial function by the effects of ROS on nitric oxide, and similar mechanisms may be present in COPD [118].

Physiological stress

COPD patients are exposed to hypoxia, either sustained hypoxia in patients with severe disease or intermittent hypoxia during exercise or exacerbations. Hypoxia may influence atherogenesis through a number of mechanisms, including enhancing systemic inflammation and oxidative stress, upregulating cell adhesion molecules and inducing haemodynamic stress [119–121]. Increased foam cell production also occurs when macrophages are exposed to hypoxic conditions [119]. Hypoxia has been shown to upregulate the cellular adhesion molecules on endothelial cells [120] and CRP also increases in response to hypoxia [121]. Hypoxia also induces haemodynamic stress [122], (*i.e.* an increase in heart rate and cardiac index), reduces renal blood flow and activates the renin-angiotensin system, resulting in increased peripheral vasoconstriction and oxidative stress [123].

Activation of the sympathetic nervous system is associated with increased risk of cardiovascular disease [124]. COPD is associated with sympathetic nervous system activation [125], which may therefore contribute to the cardiovascular morbidity and mortality observed in patients with COPD. The disease is also associated with reduced heart rate variability, a marker of abnormal cardiac autonomic regulation, which has been found to predict mortality in elderly people [126, 127].

Clinical assessment of cardiovascular disease in COPD

Given the weight of evidence supporting the increased cardiovascular risk associated with COPD, focus has turned to researching both specific mechanisms and prediction of cardiovascular events in this condition. Assessments of cardiovascular function vary from biochemical measures to imaging modalities with both clinical and research applications.

Cardiovascular risk scores

For over 20 years, systemic inflammation has been related to cardiovascular morbidity and mortality. Measurement of CRP is known to predict cardiovascular events not only in high-risk, post-acute coronary syndrome populations but also in healthy individuals [87, 88]. The Framingham Risk Score, the most widely used tool for predicting risk of cardiovascular events, is improved by adding CRP to prediction models comprising traditional risk factors [128]. As systemic inflammation is associated with disease severity in COPD, this may prove useful in large COPD cohorts.

More recently, LEE *et al.* [129] reported that global cardiovascular risk scores using a combination of traditional risk factors predicted mortality regardless of the severity of airflow limitation and predicted mortality better in patients with COPD than lung function alone.

History and ECG

Assessment of symptoms particularly in exacerbations of COPD can be difficult, as many of the symptoms associated with exacerbations of COPD can mimic or mask cardiovascular symptoms.

MCALLISTER *et al.* [56] prospectively recruited patients who attended hospital with an exacerbation of COPD and took a detailed chest pain history. 51% of these patients had chest pain, and 40% of these had pain recognised as high-risk and more indicative of myocardial ischaemia (*e.g.* “like a pressure”, exertional or radiating to the arm or jaw). Interestingly, patients with these symptoms did not have increased troponin levels, suggesting that chest pain as a symptom in the context of an exacerbation of COPD may not be useful as a predictor of myocardial events in these patients.

In the same study, ECGs were reviewed on admission. Abnormal ECGs were common in patients attending with exacerbations of COPD but were, for the most part, not associated with raised troponin levels. Both in this study and another in stable COPD patients [130], ECGs were coded and scored (using the Minnesota code and the Cardiac Injury Infarction Score (CIIS)). In both studies, patients with COPD had a high proportion of ECG changes suggestive of underlying cardiovascular disease. In the latter study, there was an association between the CIIS and the severity of airflow limitation in COPD patients, suggesting an increased likelihood of underlying cardiovascular disease in those patients with more severe lung disease.

Biochemical measurements

MCALLISTER *et al.* [56] found that one in 12 patients attending hospital with an exacerbation of COPD had a raised troponin level, consistent with myocardial damage. Similarly, in a consecutive case series of 71 patients admitted to an intensive care unit with a severe exacerbation of COPD and respiratory failure, 18% had a raised troponin level [131], and in another large consecutive case series of 250 patients with an exacerbation of COPD, CHANG *et al.* [54] found 17% of patients had a raised troponin level. The significance of a raised troponin level in exacerbations of COPD is not clearly established. Such patients have physiological stressors such as tachycardia and hypoxia, which may cause subendocardial events rather than transmural events. However, CHANG *et al.* [54] also reported that a raised troponin level predicted mortality at 30 days (OR 6.3), even after adjustment for other measures of disease severity. HOISETH *et al.* [55] followed patients for a median of 2 years after exacerbation of COPD and found that having raised troponin on admission was associated with increased mortality. More recently, SØYSETH *et al.* [132] studied both stable COPD patients and during exacerbations and found that patients had a four-fold increase in high-sensitivity cardiac troponin T (hs-cTNT) level during exacerbations in comparison to the stable state. In addition, higher hs-cTNT was associated with COPD severity.

As well as markers of myocardial injury, markers of left ventricular dysfunction are now used to try and separate the causes of breathlessness, which are difficult to determine clinically. CHANG *et al.* [54] also measured NT-proBNP, a biomarker associated with increased mortality in stable and acute heart disease [133]. As with troponin, NT-proBNP predicted 30-day mortality in patients admitted with exacerbations of COPD [54]. There is also evidence of a strong association between NT-proBNP levels and ventricular dysfunction in COPD [132].

The mechanisms leading to the release of these biomarkers is currently unclear. During exacerbations, the presence of systemic inflammatory mediators may result in myocardial damage, along with the subendocardial ischaemia associated with physiological stressors to both the left and right heart, as mentioned earlier. In addition, tachycardia and changes in intrathoracic pressure on a background of subclinical cardiac dysfunction may stimulate release of markers of ventricular dysfunction.

Echocardiography

Heart failure is common in patients with COPD and COPD is common in patients with heart failure. MACCHIA *et al.* [134] reported a prevalence of heart failure assessed by echocardiography in 17% COPD patients. As described previously, in a study of 405 patients in primary care with COPD, 20% received a new diagnosis of heart failure after investigation [59]. Subclinical left ventricular and right ventricular systolic dysfunction can occur even in patients with mild airways obstruction [135].

In a large population-based study, the Multi-Ethnic Study of Atherosclerosis (MESA), emphysema severity assessed using quantitative CT scanning was associated with impaired left ventricular filling, reduced stroke volume and lower cardiac output [136].

As described previously, a concomitant diagnosis of heart failure and COPD increases both morbidity and mortality [134, 137]. However, echocardiography can be difficult in COPD. Echocardiography windows are restricted due to hyperinflation and the proportion of unsatisfactory studies increases with disease severity [59, 138].

PWV and pulse wave analysis

Arterial stiffness can be measured using several techniques, all of which employ similar equipment. The gold standard method is PWV [95, 139]. Carotid–femoral PWV measures the speed of the pulse wave across the aorta, which is responsible for most of the pathophysiological effects of increased arterial stiffness. Large vessels cushion the pressure created in systole by ventricular contraction and this function is reduced in stiff arteries, resulting in a faster pulse wave. Carotid–femoral (aortic) PWV is increased with increased arterial stiffness.

PWV is calculated as $D/\Delta t$. D is the surface distance between the two recording points (*i.e.* the carotid pulse and the femoral pulse). Using applanation tonometry at the carotid and femoral arteries, a pressure waveform is recorded. An intersecting tangent method to identify the onset of the wave and the difference in transit time to the femoral and carotid arteries is taken as Δt (fig. 5). Carotid–femoral PWV is predictive of cardiovascular events in healthy individuals as well as being associated with mortality in patients with ischaemic heart disease [96, 140]. It is also possible to measure carotid–radial PWV across the brachial artery. However, unlike aortic PWV, measurement of arterial stiffness across this muscular artery is not associated with CIMT, a noninvasive measure of atherosclerotic plaque burden. In addition, it is neither associated with cardiovascular events nor mortality [95, 141].

Pulse wave analysis is another noninvasive measure of arterial stiffness. This relies on wave reflection from bifurcating vessels. In compliant blood vessels, the pulse wave is reflected back to the aortic root in diastole. In stiff blood vessels, the wave is reflected earlier, often during systole, augmenting the systolic pressure. Time to wave reflection (T_r) is reduced in the presence of stiff arteries. Using a radial pressure waveform measured by applanation tonometry, the difference in the systolic peak from the peak caused by the inflected waveform is the augmentation pressure (AP) (fig. 6). AP expressed as a percentage of pulse pressure is called the augmentation index (AIx). AP and AIx are increased in the presence of stiff arteries. The main determinants of AIx are age, heart rate (it is often corrected for this), diastolic blood pressure and aortic PWV. AIx-75 is the standard measure of AIx corrected for a heart rate of 75 beats·min⁻¹ and is calculated using a transfer function. Pulse wave analysis does not have the same predictive value as aortic PWV but it is still a useful measure of arterial stiffness as it requires little technical expertise. AIx does predict mortality in end-stage renal disease and cardiovascular events [142, 143].

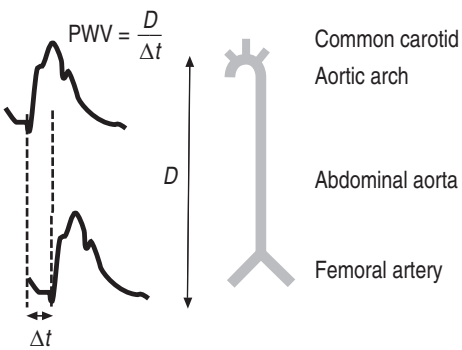


Figure 5. Measurement of carotid–femoral pulse wave velocity (PWV) using the intersecting tangent method, where D is the surface distance between the two recording points and Δt is the difference in transit time to the carotid and femoral arteries.

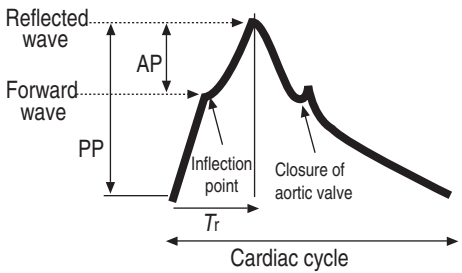


Figure 6. An example of a radial pressure waveform. The augmentation index is calculated as $AP/PP \times 100$, where AP is augmentation pressure and PP is pulse pressure. T_r : time to wave transfer.

Both these measures of arterial stiffness show increased arterial stiffness in COPD patients. SABIT *et al.* [144] measured aortic PWV in both COPD patients and controls, and showed increased arterial stiffness in COPD. This was confirmed in a study of COPD patients and controls with no history of cardiovascular disease matched for cigarette smoke exposure [100]. In a cohort of COPD patients, carotid–radial PWV was associated with CT-quantified emphysema severity, independent of traditional risk factors [31]. In a further study, AP was increased and Tr was reduced in patients with COPD in comparison with matched controls [145]. AP was associated with serum CRP levels in the COPD patients, suggesting that systemic inflammation may have a role in this vascular dysfunction.

CT scanning

Recent studies have suggested that the arterial stiffness associated with COPD may in part be due to increased vascular calcification and that vascular calcification is associated with emphysema severity [146–148]. DRANSFIELD *et al.* [146] assessed CT-quantified emphysema and thoracic aortic calcification in a population of subjects with and without COPD, and found an independent association between these measures. In a population-based study, McALLISTER *et al.* [148] reported that reduced FEV₁ was associated with increased distal aortic calcification. BOLTON *et al.* [147] found an association between aortic calcification and aortic PWV in a cohort of COPD patients.

The large vessel calcification in COPD mirrors the medial elastocalcinosis seen in large vessels as a feature of normal ageing [106]. As the elastin in the vessel wall is degraded, the calcium content is thought to increase. Thus, measures of vascular calcification in the aorta may also be a reflection of elastin degradation.

A combination of positron emission tomography and CT is now a standard imaging modality used in staging lung cancer. There is increased fluorodeoxyglucose (FDG) uptake in areas of inflammation [149]. COULSON *et al.* [149] measured the FDG uptake in the aortas of COPD patients and controls. They showed increased inflammation in the large blood vessels of patients with COPD in comparison to controls, which may be a mechanism for the increased arterial stiffness described above.

Measures of endothelial function

FMD is a measure of arterial vasomotor function using ultrasound to assess the dilatation of the brachial artery following arterial occlusion [97]. Subsequent reactive hyperaemia is primarily dependent on the release of nitric oxide, a potent vasodilator, from the endothelium. BARR *et al.* [98] found that impaired FMD was associated with both airflow obstruction and emphysema severity in former smokers with and without COPD. EICKHOFF *et al.* [99] showed impaired FMD in patients with COPD, compared with both healthy controls and smokers with normal lung function. They also showed associations with lung function and markers of systemic inflammation, including CRP, and concluded that systemic inflammation may play a role in vascular dysfunction in COPD.

Forearm venous occlusion plethysmography is a minimally invasive technique used to study endothelial vasomotor function in humans [150]. Forearm blood flow is measured using a mercury-in-silastic strain gauge that encircles the widest part of the forearm. A pressure cuff is attached to the upper arm and this is set to inflate above venous pressure. The strain gauge records a linear increase in forearm volume (as there is an increase in resistance as the gauge stretches with forearm circumference), which is proportional to arterial inflow. This change in volume is predominantly due to blood flow through skeletal muscle in the forearm. Using this technique, impairment of endothelial function has been demonstrated in many conditions, including stable ischaemic heart disease, cigarette smoking, hypercholesterolaemia and type 1 diabetes [151–154]. In a study that described increased arterial stiffness in patients with COPD in comparison to controls, MACLAY *et al.* [100] showed no difference in either venous occlusion plethysmography

nor release of t-PA from the forearm endothelium between COPD patients and control subjects matched for smoking and age, suggesting that endothelial function was abnormal in COPD, as it was in smokers, but with no additional effect of COPD on endothelial function. However, there may be abnormalities in endothelial function of conduit vessels like the brachial artery (as measured using FMD) in COPD that are not present in resistance vessels (as measured using venous occlusion plethysmography).

Treatment of cardiovascular comorbidities in COPD patients

Coronary artery disease

There is a lack of evidence for determining treatment of CAD in COPD patients as there are no prospective, randomised studies investigating treatments for CAD comparing patients with and without COPD. With the exception of the use of β -blockers in COPD, treatment of CAD in COPD patients is largely undiscussed in guidelines for ischaemic heart disease treatment [155–157].

Primary intervention strategies for individuals at risk of pulmonary disease are based on modifiable risk factors including smoking, hypertension, obesity and healthy diet, abnormal lipids, and physical activity [9]. Based on the evidence presented in this chapter, it may be that COPD should be considered an independent risk factor for CAD. The application of these measures related to healthy lifestyle is also appropriate for COPD and may have an impact on COPD prevalence.

Secondary prevention of CAD includes treatment with anti-platelet therapy (aspirin, clopidogrel and statin) and angiotensin-converting enzyme (ACE) inhibitors. These treatments should be applied in a similar way to CAD patients with or without COPD. There is recent evidence from a number of retrospective pharmacoepidemiological studies that statins reduce all-cause and COPD mortality, exacerbations, hospitalisations and intubations, and slow the decline in lung function in COPD (fig. 7) [164]. ACE inhibitors and angiotensin receptor blockers in combination with statins may reduce hospitalisation for COPD and MI, and all-cause mortality and death from MI in COPD patients [158]. Prospective studies of the effect of statin therapy in COPD are in progress to determine the effects of statins on outcomes in COPD patients.

β -blockers have been shown to improve prognosis by 30% in post-MI trials [165]. Meta-analysis of the

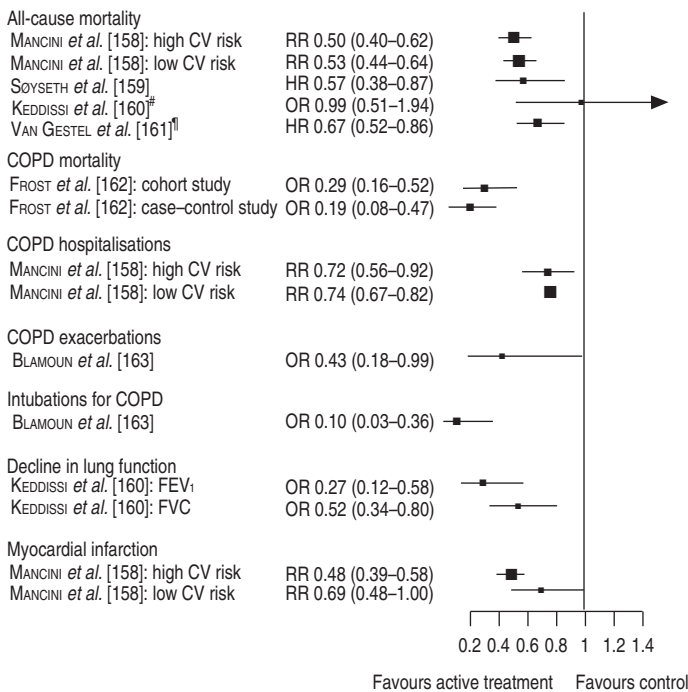


Figure 7. Forest plot of effect estimates of statins for odds ratios (ORs), hazard ratios (HRs) and relative risks (RRs) with 95% confidence intervals. Where available, adjusted estimates were used. Values <1 indicate a better outcome with statin therapy. Box size is proportional to precision of the estimate. Whiskers represent 95% confidence intervals. CV: cardiovascular; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity. [#]: mortality was only given for the whole cohort, which included 24% of patients with restrictive rather than obstructive spirometry findings; [†]: 10-year mortality (mortality at 30 days not shown). Reproduced and modified from [164] with permission from the publisher.

effects of β -blockers on mortality showed a relative risk reduction in mortality of 24% with secondary preventive treatment [166]. β -blockers are, therefore, a first-line therapy to improve not only symptoms but also cardiac outcomes, particularly in post-MI patients with reduced left ventricular function [156]. β -blockers are, however, under-utilised in patients with previous MI and COPD because of a perceived contraindication of worsening airflow limitation [167, 168]. In fact, cardioselective β -blockers are well tolerated in patients with cardiac disease and concomitant COPD, and there is no good evidence that β -blockers worsen respiratory symptoms or airflow limitation in COPD patients. Indeed, in a retrospective study in patients admitted with an acute exacerbation of COPD as a primary diagnosis, those who had received β -blocker treatment had reduced mortality (OR 0.39) [169]. In patients who underwent major cardiovascular surgery, those with COPD who were treated with cardioselective β -blockers had a lower 30-day (OR 0.37) and long-term mortality (HR 0.73) compared with those who did not receive this treatment [161]. A recent study in the Netherlands using general practice electronic records, which included 2,230 patients aged 45 years and older with a diagnosis of COPD, also suggested that β -blocker use was associated with decreased mortality (HR 0.68, 95% CI 0.56–0.83) and exacerbation frequency (HR 0.71, 95% CI 0.60–0.83). Thus, β -blockers may reduce the risk of exacerbation and improve survival in patients with COPD. Under-utilisation of β -blockers has also been linked to poor outcomes after MI in patients with reduced left ventricular function [170]. Thus, accumulating evidence from trials and meta-analysis indicates that cardioselective β -blockers (e.g. atenolol, bisoprolol or metoprolol) should not be withheld in patients with COPD and, therefore, treatment of CAD should be treated in the same way in patients with and without COPD.

Myocardial revascularisation is a key treatment in CAD. Percutaneous coronary intervention (PCI) is now the most commonly used perfusion procedure [157]. In a recent study of 9,877 consecutive patients undergoing their first elective PCI or coronary artery bypass grafting, COPD was present in 2.4% of the subjects and increased the adjusted risk for all-cause and cardiac mortality by 36% and 48%, respectively [171]. A further study in 10,994 patients treated with PCI found that COPD was present in 11.3% of subjects and resulted in an adjusted HR for long-term mortality of 2.16 (95% CI 1.81–2.56, $p < 0.0001$) [172]. The presence of COPD is also associated with poor outcome following PCI during acute MI [173]. These studies indicate that COPD patients in most clinical settings are at higher risk of adverse events following revascularisation therapy.

Treatment of heart failure in COPD patients

As for CAD, cardioselective β -blockade is well established as an important treatment in heart failure and is considered safe in COPD patients with heart failure although, again, this treatment is under-used in COPD patients [174].

Treatment of hypertension in COPD patients

In view its high prevalence in COPD, hypertension should be actively looked for in COPD patients and aggressively managed. There is no evidence that hypertension should be treated differently in COPD patients than in those patients without COPD.

Treatment of arrhythmias in COPD patients

Management of arrhythmias in COPD patients should generally be similar to those without COPD, although adenosine can cause respiratory distress and should be avoided in COPD patients [175]. In particular, cardioselective β -blockers should not be withheld, as indicated for a stable COPD patient.

Effects of COPD treatment on cardiovascular morbidity and mortality

Smoking cessation is an important primary and secondary preventative measure in COPD patients. Smoking cessation has an effect on blood pressure and heart rate, and reduces the risk of stroke and CAD to that of never-smokers between 5 and 15 years after smoking cessation. In the

Lung Health Study, in patients with mild-to-moderate COPD, smoking cessation was associated with a 32% reduction in all-cause mortality and a 45% reduction in cardiovascular mortality as a result of a reduction in cardiovascular events [176].

Long-term oxygen therapy has been shown to reduce mortality in COPD patients with respiratory failure [177, 178]. There is no evidence that long-term oxygen therapy reduces cardiac mortality.

Pulmonary rehabilitation has been shown to reduce hospital admissions, exacerbations and mortality in COPD patients, but it is not clear whether this is as a result of reduced cardiac morbidity/mortality [179]. However, endurance training has beneficial cardiovascular effects, including decreasing resting heart rate, increasing diastolic dimensions and improving left ventricular function [180]. A small case-control study has also shown that 7-week pulmonary rehabilitation treatment produced a significant reduction in PWV, a measure of arterial stiffness, largely due to a reduction in systolic blood pressure sufficient to reduce cardiovascular morbidity and mortality by at least 13% [181].

Recent randomised controlled trials of inhaled pharmacotherapy in COPD have suggested that this could affect survival. In the TORCH study, in which 6,184 moderate-to-severe COPD patients were randomised to either long-acting β -agonists (LABA), inhaled corticosteroids (ICS), a combination of ICS and LABA, or placebo, there was a borderline increase in survival ($p=0.052$) with the combination of ICS and LABA [40]. A *post hoc* analysis in the TORCH study showed fewer cardiovascular events within the ICS/LABA treatment group (ICS/LABA 11.3%, fluticasone propionate 13.8%, salmeterol 13.4%, placebo 14.6%) [182]. In the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial, in 5,993 COPD patients randomised to receive tiotropium or placebo, there was a non-statistically significant reduction in all-cause mortality *versus* placebo (HR 0.89, 95% CI 0.79–1.02) [183]. However, in a *post hoc* analysis, there was a significant reduction in mortality after 4 years of treatment (HR 0.84, 95% CI 0.73–0.97; $p=0.016$) [182–184]. There was also a reduction in cardiac mortality (relative risk (RR) 0.86, 95% CI 0.75–0.99) and myocardial infarction (RR 0.71, 95% CI 0.52–0.99) [184].

Randomised controlled trials of ICS *versus* control have not shown evidence of a reduction of cardiovascular events, particularly MI [185]. In one randomised controlled trial, however, performed in 249 COPD patients randomised to receive a fluticasone/salmeterol combination inhaler or placebo, there was a decrease in PWV after 12 weeks of treatment that did not reach statistical significance [186].

Statement of Interest

W. MacNee has acted in an advisory capacity for GSK, Pfizer, Novartis and Almirall. He has received payment from GSK and Pfizer for research programmes and clinical activities, and has also received payments from Boehringer-Ingelheim, GSK, AstraZeneca, Novartis and Janssen to travel to meetings and/or present at conferences.

References

1. Camilli AE, Robbins DR, Lebowitz MD. Death certificate reporting of confirmed airways obstructive disease. *Am J Epidemiol* 1991; 133: 795–800.
2. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005; 128: 2640–2646.
3. Friedman GD, Klatzky AL, Siegel AB. Lung function and risk of myocardial infarction and sudden cardiac death. *N Engl J Med* 1976; 294: 1071–1075.
4. Ebi-Kryston KL, Hawthorne VM, Rose G, *et al.* Breathlessness, chronic bronchitis and reduced pulmonary function as predictors of cardiovascular disease mortality among men in England, Scotland and the United States. *Int J Epidemiol* 1989; 18: 84–88.
5. Ebi-Kryston K. Respiratory symptoms and pulmonary function as predictors of 10-year mortality from respiratory disease, cardiovascular disease, and all causes in the Whitehall Study. *J Clin Epidemiol* 1988; 41: 251–260.
6. Gulsvik A, Hansteen V, Sivertsen E. Cardiac arrhythmias in patients with serious pulmonary diseases. *Scand J Respir Dis* 1978; 59: 154–159.

7. Hole D, Watt G, Davey-Smith G, *et al.* Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313: 711–715.
8. Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962–969.
9. Yusuf S, Hawken S, Ounpuu S, *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364: 937–952.
10. Marcus EB, Curb JD, MacLean CJ, *et al.* Pulmonary function as a predictor of coronary heart disease. *Am J Epidemiol* 1989; 129: 97–104.
11. Schunemann H, Dorn J, Grant B, *et al.* Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 2000; 118: 656–664.
12. Sin DD, Wu L, Man SFP. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005; 127: 1952–1959.
13. Sin DD, Anthonisen NR, Soriano JB, *et al.* Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; 28: 1245–1257.
14. Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med* 2006; 100: 115–122.
15. Anthonisen NR, Connett JE, Kiley JP, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁. The Lung Health Study. *JAMA* 1994; 272: 1497–1505.
16. Soriano JB, Visick GT, Muellerova H, *et al.* Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; 128: 2099–2107.
17. Curkendall SM, DeLuise C, Jones JK, *et al.* Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006; 16: 63–70.
18. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; 107: 1514–1519.
19. Feary JR, Rodrigues LC, Smith CJ, *et al.* Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010; 65: 956–962.
20. Agusti A, Calverley PMA, Celli B, *et al.* Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respiratory Research* 2010; 11: 122.
21. Barr RG, Celli BR, Mannino DM, *et al.* Comorbidities, patient knowledge, and disease management in a national sample of patients with COPD. *Am J Med* 2009; 122: 348–355.
22. Johnston A, Mannino D, Hagan G, *et al.* Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort. *Thorax* 2008; 63: 599–605.
23. Curkendall S, Lanes S, de Luise C, *et al.* Chronic obstructive pulmonary disease severity and cardiovascular outcomes. *Eur J Epidemiol* 2006; 21: 803–813.
24. Hospers JJ, Postma DS, Rijcken B, *et al.* Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000; 356: 1313–1317.
25. Knuiman MW, James AL, Divitini ML, *et al.* Lung function, respiratory symptoms, and mortality: results from the Busselton Health Study. *Ann Epidemiol* 1999; 9: 297–306.
26. Sin DD, Man SFP. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005; 2: 8–11.
27. Engström G, Hedblad B, Janzon L, *et al.* Respiratory decline in smokers and ex-smokers—an independent risk factor for cardiovascular disease and death. *J Cardiovasc Risk* 2000; 7: 267–272.
28. Tockman M, Pearson J, Fleg J, *et al.* Rapid decline in FEV₁. A new risk factor for coronary heart disease mortality. *Am J Respir Crit Care Med* 1995; 151: 390–398.
29. Zureik M, Benetos A, Neukirch C, *et al.* Reduced pulmonary function is associated with central arterial stiffness in men. *Am J Respir Crit Care Med* 2001; 164: 2181–2185.
30. Iwamoto H, Yokoyama A, Kitahara Y, *et al.* Airflow limitation in smokers is associated with subclinical atherosclerosis. *Am J Respir Crit Care Med* 2009; 179: 35–40.
31. McAllister DA, Maclay JD, Mills NL, *et al.* Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 1208–1214.
32. Hadi HAR, Zubaid M, Al Mahmeed W, *et al.* Prevalence and prognosis of chronic obstructive pulmonary disease among 8167 Middle Eastern patients with acute coronary syndrome. *Clin Cardiol* 2010; 33: 228–235.
33. Wakabayashi K, Gonzalez MA, Delhaye C, *et al.* Impact of chronic obstructive pulmonary disease on acute-phase outcome of myocardial infarction. *Am J Cardiol* 2010; 106: 305–309.
34. Hawkins NM, Huang Z, Pieper KS, *et al.* Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial infarction: analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). *Eur J Heart Fail* 2009; 11: 292–298.
35. Salisbury AC, Reid KJ, Spertus JA. Impact of chronic obstructive pulmonary disease on post-myocardial infarction outcomes. *Am J Cardiol* 2007; 99: 636–641.

36. Behar S, Panosh A, Reicher-Reiss H, *et al*. Prevalence and prognosis of chronic obstructive pulmonary disease among 5,839 consecutive patients with acute myocardial infarction. SPRINT Study Group. *Am J Med* 1992; 93: 637–641.
37. Bursi F, Vassallo R, Weston SA, *et al*. Chronic obstructive pulmonary disease after myocardial infarction in the community. *Am Heart J* 2010; 160: 95–101.
38. Soriano JB, Rigo F, Guerrero D, *et al*. High prevalence of undiagnosed airflow limitation in patients with cardiovascular disease. *Chest* 2010; 137: 333–340.
39. Anthonisen NR, Skeans MA, Wise RA, *et al*. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; 142: 233–239.
40. Calverley P, Anderson J, Celli B, *et al*. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
41. McGarvey L, John M, Anderson J, *et al*. Ascertainment of cause-specific mortality in COPD – operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; 62: 411–415.
42. McGarvey LP, Magder S, Burkhardt D, *et al*. Cause-specific mortality adjudication in the UPLIFT COPD trial: findings and recommendations. *Respir Med* 2012; 106: 515–521.
43. Vilkinan S, Keistinen T, Tuuponen T, *et al*. Survival and cause of death among elderly chronic obstructive pulmonary disease patients after first admission to hospital. *Respiration* 1997; 64: 281–284.
44. Engström G, Wollmer P, Hedblad B, *et al*. Occurrence and prognostic significance of ventricular arrhythmia is related to pulmonary function: a study from “men born in 1914,” Malmö, Sweden. *Circulation* 2001; 103: 3086–3091.
45. Garcia-Aymerich J, Farrero E, Félez MA, *et al*. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003; 58: 100–105.
46. Celli B, Cote C, Marin J, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
47. Stavem K, Aaser E, Sandvik L, *et al*. Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males. *Eur Respir J* 2005; 25: 618–625.
48. Stone IS, Barnes NC, Petersen SE. Chronic obstructive pulmonary disease: a modifiable risk factor for cardiovascular disease? *Heart* 2012; 98: 1055–1062.
49. Sidney S, Sorel M, Quesenberry C, *et al*. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005; 128: 2068–2075.
50. Patel AR, Donaldson GC, Mackay AJ, *et al*. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest* 2012; 141: 851–857.
51. Donaldson GC, Hurst JR, Smith CJ, *et al*. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.
52. Harvey MG, Hancox RJ. Elevation of cardiac troponins in exacerbation of chronic obstructive pulmonary disease. *Emerg Med Australas* 2004; 16: 212–215.
53. Brekke PH, Omeland T, Holmedal SH, *et al*. Troponin T elevation and long-term mortality after chronic obstructive pulmonary disease exacerbation. *Eur Respir J* 2008; 31: 563–570.
54. Chang CL, Robinson SC, Mills GD, *et al*. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax* 2011; 66: 764–768.
55. Hoiseith AD, Neukamm A, Karlsson BD, *et al*. Elevated high-sensitivity cardiac troponin T is associated with increased mortality after acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2011; 66: 775–781.
56. McAllister DA, Maclay JD, Mills NL, *et al*. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. *Eur Respir J* 2012; 39: 1097–1103.
57. de Miguel-Díez J, Carrasco-Garrido P, Rejas-Gutierrez J, *et al*. The influence of heart disease on characteristics, quality of life, use of health resources, and costs of COPD in primary care settings. *BMC Cardiovasc Disord* 2010; 10: 8.
58. Agustí A, Edwards LD, Rennard SI, *et al*. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7: e37483.
59. Rutten FH, Cramer MJM, Grobbee DE, *et al*. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005; 26: 1887–1894.
60. Mascarenhas J, Lourenco P, Lopes R, *et al*. Chronic obstructive pulmonary disease in heart failure. Prevalence, therapeutic and prognostic implications. *Am Heart J* 2008; 155: 521–525.
61. Kwon BJ, Kim DB, Jang SW, *et al*. Prognosis of heart failure patients with reduced and preserved ejection fraction and coexistent chronic obstructive pulmonary disease. *Eur J Heart Fail* 2010; 12: 1339–1244.
62. De Blois J, Simard S, Atar D, *et al*. COPD predicts mortality in heart failure: the Norwegian Heart Failure Registry. *J Card Fail* 2010; 16: 225–229.
63. Mentz RJ, Fiuzat M, Wojdyla DM, *et al*. Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: findings from OPTIMIZE-HF. *Eur J Heart Fail* 2012; 14: 395–403.
64. Rusinaru D, Saaidi I, Godard S, *et al*. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *Am J Cardiol* 2008; 101: 353–358.
65. Iversen KK, Kjaergaard J, Akkan D, *et al*. The prognostic importance of lung function in patients admitted with heart failure. *Eur J Heart Fail* 2010; 12: 685–691.

66. Engström G, Melander O, Hedblad B. Population-based study of lung function and incidence of heart failure hospitalisations. *Thorax* 2010; 65: 633–638.
67. Agarwal SK, Heiss G, Barr RG, *et al.* Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. *Eur J Heart Fail* 2012; 14: 414–422.
68. Kee K, Naughton MT. Heart failure and the lung. *Circ J* 2010; 74: 2507–2516.
69. MacLay JD, McAllister DA, Rabinovich R, *et al.* Systemic elastin degradation in chronic obstructive pulmonary disease. *Thorax* 2012; 67: 606–612.
70. Mapel DW, Dedrick D, Davis K. Trends and cardiovascular co-morbidities of COPD patients in the Veterans Administration Medical System, 1991–1999. *COPD* 2005; 2: 35–41.
71. Buch P, Friberg J, Scharling H, *et al.* Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J* 2003; 21: 1012–1016.
72. Lahousse L, van den Bouwhuijsen Q, Loth DW, *et al.* Chronic obstructive pulmonary disease and lipid core carotid artery plaques in the elderly: the Rotterdam Study. *Am J Respir Crit Care Med* 2012; [Epub ahead of print DOI: 10.1164/rccm.201206-1046OC].
73. Barr RG, Ahmed FS, Carr JJ, *et al.* Subclinical atherosclerosis, airflow obstruction and emphysema: the MESA lung study. *Eur Respir J* 2012; 39: 846–854.
74. Basili S, Ferroni P, Vieri M, *et al.* Lipoprotein(a) serum levels in patients affected by chronic obstructive pulmonary disease. *Atherosclerosis* 1999; 147: 249–252.
75. Walter RE, Wilk JB, Larson MG, *et al.* Systemic inflammation and COPD: the Framingham Heart Study. *Chest* 2008; 133: 19–25.
76. Incalzi RA, Fuso L, De Rosa M, *et al.* Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 2794–2800.
77. Holguin F, Folch E, Redd S, *et al.* Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005; 128: 2005–2011.
78. Hu FB, Meigs JB, Li TY, *et al.* Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004; 53: 693–700.
79. Bolton CE, Evans M, Ionescu AA, *et al.* Insulin resistance and inflammation – a further systemic complication of COPD. *COPD* 2007; 4: 121–126.
80. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ* 2006; 174: 801–809.
81. ten Hacken NH. Physical inactivity and obesity: relation to asthma and chronic obstructive pulmonary disease? *Proc Am Thorac Soc* 2009; 6: 663–667.
82. Laveneziana P, Palange P, ERS Research Seminar Faculty. Physical activity, nutritional status and systemic inflammation in COPD. *Eur Respir J* 2012; 40: 522–529.
83. Burke AP, Farb A, Malcom GT, *et al.* Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997; 336: 1276–1282.
84. Libby P, Ridker PM, Hansson GK, *et al.* Inflammation in atherosclerosis. *JAC* 2009; 54: 2129–2138.
85. van der Wal AC, Becker AE. Atherosclerotic plaque rupture – pathologic basis of plaque stability and instability. *Cardiovasc Res* 1999; 41: 334–344.
86. Pasterkamp G, Schoneveld AH, Van Der Wal AC, *et al.* Inflammation of the atherosclerotic cap and shoulder of the plaque is a common and locally observed feature in unruptured plaques of femoral and coronary arteries. *Arterioscler Thromb Vasc Biol* 1999; 19: 54–58.
87. Koenig W, Sund M, Frohlich M, *et al.* C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999; 99: 237–242.
88. Ridker P, Rifai N, Rose L, *et al.* Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347: 1557–1565.
89. Ridker P, Danielson E, Fonseca F, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. *N Engl J Med* 2008; 359: 2195–2207.
90. Pinto-Plata VM, Müllerova H, Toso JF, *et al.* C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax* 2006; 61: 23–28.
91. Gan WQ, Man SFP, Senthilvelan A, *et al.* Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574–580.
92. Man SFP, Connett JE, Anthonisen NR, *et al.* C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax* 2006; 61: 849–853.
93. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005; 111: 3481–3488.
94. Smeeth L, Thomas SL, Hall AJ, *et al.* Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004; 351: 2611–2618.
95. Laurent S, Cockcroft J, Van Bortel L, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27: 2588–2605.
96. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness. *J Am Coll Cardiol* 2010; 55: 1318–1327.

97. Corretti MC, Anderson TJ, Benjamin EJ, *et al.* Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002; 39: 257–265.
98. Barr RG, Mesia-Vela S, Austin JHM, *et al.* Impaired flow-mediated dilation is associated with low pulmonary function and emphysema in ex-smokers: the Emphysema and Cancer Action Project (EMCAP) study. *Am J Respir Crit Care Med* 2007; 176: 1200–1207.
99. Eickhoff P, Valipour A, Kiss D, *et al.* Determinants of systemic vascular function in patients with stable COPD. *Am J Respir Crit Care Med* 2008; 178: 1211–1218.
100. MacLay JD, McAllister DA, Mills NL, *et al.* Vascular dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 180: 513–520.
101. Gerstein HC, Mann JF, Yi Q, *et al.* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286: 421–426.
102. Solomon SD, Lin J, Solomon CG, *et al.* Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. *Circulation* 2007; 116: 2687–2693.
103. Casanova C, De Torres JP, Navarro J, *et al.* Microalbuminuria and hypoxemia in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 182: 1004–1010.
104. van Dijk EJ, Vermeer SE, de Groot JC, *et al.* Arterial oxygen saturation, COPD, and cerebral small vessel disease. *J Neurol Neurosurg Psychiatr* 2004; 75: 733–736.
105. Dodd JW, Chung AW, Van Den Broek MD, *et al.* Brain structure and function in chronic obstructive pulmonary disease: a multimodal cranial magnetic resonance imaging study. *Am J Respir Crit Care Med* 2012; 186: 240–245.
106. Atkinson J. Age-related medial elastocalcinosis in arteries: mechanisms, animal models, and physiological consequences. *J Appl Physiol* 2008; 105: 1643–1651.
107. Black PN, Ching PST, Beaumont B, *et al.* Changes in elastic fibres in the small airways and alveoli in COPD. *Eur Respir J* 2008; 31: 998–1004.
108. Patel BD, Loo WJ, Tasker AD, *et al.* Smoking related COPD and facial wrinkling: is there a common susceptibility? *Thorax* 2006; 61: 568–571.
109. Aldonyte R, Jansson L, Piitulainen E, *et al.* Circulating monocytes from healthy individuals and COPD patients. *Respir Res* 2003; 4: 11.
110. Yasmin, McEniery CM, Wallace S, *et al.* Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; 25: 372.
111. Yasmin, McEniery CM, O'Shaughnessy KM, *et al.* Variation in the human matrix metalloproteinase-9 gene is associated with arterial stiffness in healthy individuals. *Arterioscler Thromb Vasc Biol* 2006; 26: 1799–1805.
112. Chung AWY, Yang HHC, Kim JM, *et al.* Upregulation of matrix metalloproteinase-2 in the arterial vasculature contributes to stiffening and vasomotor dysfunction in patients with chronic kidney disease. *Circulation* 2009; 120: 792–801.
113. MacNee W. Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 50–60.
114. Lee YW, Kühn H, Hennig B, *et al.* IL-4-induced oxidative stress upregulates VCAM-1 gene expression in human endothelial cells. *J Mol Cell Cardiol* 2001; 33: 83–94.
115. Griendling KK, Ushio-Fukai M. Redox control of vascular smooth muscle proliferation. *J Lab Clin Med* 1998; 132: 9–15.
116. Aoki M, Nata T, Morishita R, *et al.* Endothelial apoptosis induced by oxidative stress through activation of NF- κ B: antiapoptotic effect of antioxidant agents on endothelial cells. *Hypertension* 2001; 38: 48–55.
117. Kameda K, Matsunaga T, Abe N, *et al.* Correlation of oxidative stress with activity of matrix metalloproteinase in patients with coronary artery disease. Possible role for left ventricular remodelling. *Eur Heart J* 2003; 24: 2180–2185.
118. Mills NL, Törnqvist H, Robinson SD, *et al.* Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation* 2005; 112: 3930–3936.
119. Lattimore J-DL, Wilcox I, Nakhla S, *et al.* Repetitive hypoxia increases lipid loading in human macrophages—a potentially atherogenic effect. *Atherosclerosis* 2005; 179: 255–259.
120. Ichikawa H, Flores S, Kvietys PR, *et al.* Molecular mechanisms of anoxia/reoxygenation-induced neutrophil adherence to cultured endothelial cells. *Circ Res* 1997; 81: 922–931.
121. Hartmann G, Tschöp M, Fischer R, *et al.* High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. *Cytokine* 2000; 12: 246–252.
122. Thomson AJ, Drummond G, Waring WS, *et al.* Effects of short-term isocapnic hyperoxia and hypoxia on cardiovascular function. *J Appl Physiol* 2006; 101: 809–816.
123. Skwarski KM, Morrison D, Barratt A, *et al.* Effects of hypoxia on renal hormonal balance in normal subjects and in patients with COPD. *Respir Med* 1998; 92: 1331–1336.
124. Curtis BM, O'Keefe JH Jr. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc* 2002; 77: 45–54.
125. Heindl S, Lehnert M, Criée CP, *et al.* Marked sympathetic activation in patients with chronic respiratory failure. *Am J Respir Crit Care Med* 2001; 164: 597–601.
126. Tsuji H, Venditti FJ Jr, Manders ES, *et al.* Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* 1994; 90: 878–883.

127. Volterrani M, Scalvini S, Mazzuero G, *et al.* Decreased heart rate variability in patients with chronic obstructive pulmonary disease. *Chest* 1994; 106: 1432–1437.
128. Wang TJ, Gona P, Larson MG, *et al.* Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006; 355: 2631–2639.
129. Lee H, Lee J, Lee K, *et al.* Relation between COPD severity and global cardiovascular risk in U.S. adults. *Chest* 2012; 142: 1118–1125.
130. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; 107: 1514–1519.
131. Baillard C, Boussarsar M, Fosse JP, *et al.* Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 2003; 29: 584–589.
132. Soyseth V, Brekke P, Smith P, *et al.* Statin use is associated with reduced mortality in chronic obstructive pulmonary disease. *Eur Respir J* 2007; 29: 279–283.
133. Kragelund C, Grønning B, Køber L, *et al.* N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005; 352: 666–675.
134. Macchia A, Rodriguez Moncalvo JJ, Kleinert M, *et al.* Unrecognised ventricular dysfunction in COPD. *Eur Respir J* 2012; 39: 51–58.
135. Sabit R, Bolton CE, Fraser AG, *et al.* Sub-clinical left and right ventricular dysfunction in patients with COPD. *Respir Med* 2010; 104: 1171–1178.
136. Barr R, Bluemke D, Ahmed F. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med* 2010; 362: 217–227.
137. Braunstein JB, Anderson GF, Gerstenblith G, *et al.* Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003; 42: 1226–1233.
138. Vizza C, Lynch J, Ochoa L, *et al.* Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998; 113: 576–583.
139. Mackenzie IS, Wilkinson IB, Cockcroft JR. Assessment of arterial stiffness in clinical practice. *QJM* 2002; 95: 67–74.
140. Willum-Hansen T, Staessen JA, Torp-Pedersen C, *et al.* Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; 113: 664–670.
141. Tillin T, Chambers J, Malik I, *et al.* Measurement of pulse wave velocity: site matters. *J Hypertens* 2007; 25: 383–389.
142. London GM, Blacher J, Pannier B, *et al.* Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001; 38: 434–438.
143. Williams B, Lacy PS, Thom SM, *et al.* Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113: 1213–1225.
144. Sabit R, Bolton CE, Edwards PH, *et al.* Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 1259–1265.
145. Mills NL, Miller JJ, Anand A, *et al.* Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. *Thorax* 2008; 63: 306–311.
146. Dransfield MT, Huang F, Nath H, *et al.* CT emphysema predicts thoracic aortic calcification in smokers with and without COPD. *COPD* 2010; 7: 404–410.
147. Bolton CE, McEnery CM, Raj V, *et al.* Aortic calcification, arterial stiffness and bone mineral density in patients with COPD. *Artery Res* 2011; 5: 30–36.
148. McAllister DA, Macnee W, Duprez D, *et al.* Pulmonary function is associated with distal aortic calcium, not proximal aortic distensibility. MESA lung study. *COPD* 2011; 8: 71–78.
149. Coulson JM, Rudd JHF, Duckers JM, *et al.* Excessive aortic inflammation in chronic obstructive pulmonary disease: an ¹⁸F-FDG PET pilot study. *J Nucl Med* 2010; 51: 1357–1360.
150. Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. *Br J Clin Pharmacol* 2001; 52: 631–646.
151. Heitzer T, Schlinzig T, Krohn K, *et al.* Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* 2001; 104: 2673–2678.
152. Newby D, Wright R, Labinjoh C, *et al.* Endothelial dysfunction, impaired endogenous fibrinolysis, and cigarette smoking – a mechanism for arterial thrombosis and myocardial infarction. *Circulation* 1999; 99: 1411–1415.
153. Chowieńczyk PJ, Watts GF, Cockcroft JR, *et al.* Impaired endothelium-dependent vasodilation of forearm resistance vessels in hypercholesterolaemia. *Lancet* 1992; 340: 1430–1432.
154. Johnstone MT, Creager SJ, Scales KM, *et al.* Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. *Circulation* 1993; 88: 2510–2516.
155. Graham I, Atar D, Borch-Johnsen K, *et al.* European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007; 14: Suppl. 2, S1–S113.
156. Fox K, Garcia MAA, Ardissino D, *et al.* Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006; 27: 1341–1381.

157. Wijns W, Kolh P, Danchin N, *et al.* Guidelines on myocardial revascularization. *Eur Heart J* 2010; 31: 2501–2555.
158. Mancini G, Etmann M, Zhang B, *et al.* Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006; 47: 2554–2560.
159. Søyseth V, Brekke PH, Smith P, *et al.* Statin use is associated with reduced mortality in COPD. *Eur Respir J* 2007; 29: 279–283.
160. Keddissi JJ, Younis WG, Chbeir EA, *et al.* The use of statins and lung function in current and former smoker. *Chest* 2007; 132: 1764–1771.
161. van Gestel YRBM, Hoeks SE, Sin DD, *et al.* Impact of cardioselective β -blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. *Am J Respir Crit Care Med* 2008; 178: 695–700.
162. Frost FJ, Peterssen H, Tollestrup L, *et al.* Influenza and COPD mortality prediction as pleiotropic, dose-dependent effects of statins. *Chest* 2007; 131: 1006–1012.
163. Blamoun AI, Batty GN, DeBari VA, *et al.* Statins may reduce episodes of exacerbations and the requirements for incubation in patients with COPD: evidence from a prospective cohort study. *Int J Clin Pract* 2008; 62: 1373–1378.
164. Dobler CC, Wong KK, Marks GB. Associations between statins and COPD: a systematic review. *BMC Pulm Med* 2009; 9: 32.
165. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988; 260: 2088–2093.
166. Freemantle N, Urdahl H, Eastaugh J, *et al.* What is the place of β -blockade in patients who have experienced a myocardial infarction with preserved left ventricular function? Evidence and (mis)interpretation. *Prog Cardiovasc Dis* 2002; 44: 243–250.
167. Egred M, Shaw S, Mohammad B, *et al.* Under-use of β -blockers in patients with ischaemic heart disease and concomitant chronic obstructive pulmonary disease. *QJM* 2005; 98: 493–497.
168. Olenchock BA, Fonarow GG, Pan W, *et al.* Current use of beta blockers in patients with reactive airway disease who are hospitalized with acute coronary syndromes. *Am J Cardiol* 2009; 103: 295–300.
169. Dransfield M, Rowe S, Johnson J, *et al.* β -blocker use and the risk of death in hospitalized patients with acute exacerbations of COPD. *Thorax* 2008; 63: 301–305.
170. Goldberger JJ, Bonow RO, Cuffe M, *et al.* β -blocker use following myocardial infarction: low prevalence of evidence-based dosing. *Am Heart J* 2010; 160: 435–442.
171. Nishiyama K, Morimoto T, Furukawa Y, *et al.* Chronic obstructive pulmonary disease—an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease. *Int J Cardiol* 2010; 143: 178–183.
172. Selvaraj CL, Gurm HS, Gupta R, *et al.* Chronic obstructive pulmonary disease as a predictor of mortality in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2005; 96: 756–759.
173. Campo G, Saia F, Guastaroba P, *et al.* Prognostic impact of hospital readmissions after primary percutaneous coronary intervention. *Arch Intern Med* 2011; 171: 1948–1949.
174. Rutten FH. β -blockers and their mortality benefits: underprescribed in heart failure and chronic obstructive pulmonary disease. *Future Cardiol* 2011; 7: 43–53.
175. Maedera MT, Stöckli M, Zellweger MJ. Adenosine-induced severe acute respiratory distress in chronic obstructive pulmonary disease: a myth? *Swiss Med Wkly* 2007; 137: 212.
176. Wu J, Sin DD. Improved patient outcome with smoking cessation: when is it too late? *Int J Chron Obstruct Pulmon Dis* 2011; 6: 259–267.
177. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
178. Stoller JK, Panos RJ, Krachman S, *et al.* Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. *Chest* 2010; 138: 179–187.
179. Puhan M, Scharplatz M, Troosters T, *et al.* Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009; 1: CD005305.
180. Moore RL. Cellular adaptations of the heart muscle to exercise training. *Ann Med* 1998; 30: Suppl. 1, 46–53.
181. Gale NS, Duckers JM, Enright S, *et al.* Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? *BMC Pulm Med* 2011; 11: 20.
182. Calverley PMA, Anderson JA, Celli B, *et al.* Cardiovascular events in patients with COPD: TORCH Study results. *Thorax* 2010; 65: 719–725.
183. Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
184. Celli B, Decramer M, Kesten S, *et al.* Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 180: 948–955.
185. Loke YK, Kwok CS, Singh S. Risk of myocardial infarction and cardiovascular death associated with inhaled corticosteroids in COPD. *Eur Respir J* 2010; 35: 1003–1021.
186. Dransfield MT, Cockcroft JR, Townsend RR, *et al.* Effect of fluticasone propionate/salmeterol on arterial stiffness in patients with COPD. *Respir Med* 2011; 105: 1323–1330.

Chapter 4

Diagnosis and management of heart failure in COPD

Frans H. Rutten



SUMMARY: Heart failure is common in COPD; however, it is often unrecognised. Tobacco smoking is an important cause of COPD and, indirectly, of heart failure. Heart failure and COPD share common pathways, including systemic inflammation, activation of the neurohumoral system and metabolic modulation resulting in muscle wasting and cachexia. Heart failure is an independent predictor of mortality in COPD.

The left ventricle is mainly affected in heart failure, as well as in patients with heart failure and concurrent COPD. Diagnosing heart failure in the presence of COPD is difficult because of an overlap in symptoms and signs.

Natriuretic peptides are useful for selecting COPD patients for echocardiography, which is the cornerstone for diagnosing heart failure. Therapy of heart failure in patients with COPD is, in principle, the same as in those without COPD. In patients with COPD and heart failure β_2 -agonists can be combined with cardioselective β -blockers, but anti-cholinergics seem to be a safer option. Observational data suggest that cardioselective β -blockers and statins could reduce the risk of mortality and exacerbations of COPD. However, confirmation with randomised controlled trials is required.

KEYWORDS: COPD, diagnosis, heart failure, management, prognosis, treatment

Correspondence: F.H. Rutten, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, PO Box 85060, Stratenum 6.101, 3508 AB Utrecht, The Netherlands.
Email: F.H.Rutten@umcutrecht.nl

Eur Respir Monogr 2013; 59: 50–63.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011412
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Physicians are often confronted with patients complaining of breathlessness, with approximately 40% of elderly subjects having some degree of shortness of breath [1]. Pulmonary and cardiac diseases are the main causes, and approximately 30% of cases are due to more than one cause of disease [2]. In the elderly, COPD and heart failure are the main reason for breathlessness [2].

Importantly, COPD and heart failure have largely been studied separately, with COPD in the domain of the pulmonologist and heart failure in the domain of the cardiologist. Fortunately, the interest in the interactions between both diseases has grown in the last decade [3].

Tobacco smoking is a strong common risk factor, with lung destruction resulting in COPD and systemic endothelial dysfunction causing ischaemic heart disease. Ischaemic heart disease on its

own is a major risk factor for developing heart failure. Epidemiological studies suggest that COPD on its own can also increase the risk of ischaemic heart disease, independent of age, sex, and smoking [4, 5]. Moreover, the cause of death in people with COPD is often cardiovascular [6, 7].

Both COPD and heart failure are chronic progressive diseases that lead to systemic inflammation, activation of the neurohumoral system and metabolic modulation, which eventually results in muscle wasting and cachexia [8].

Typically, heart failure develops in the presence of COPD, with COPD starting at an earlier age and having lower mortality rates than heart failure. The prevalence of heart failure is around 25% in patients with COPD aged 65 years or over, which is approximately three times higher than expected in age-matched controls from the general population [9]. Due to overlap in symptoms and signs, as much as 80% of concurrent heart failure in elderly patients with COPD remains unrecognised in daily practice, especially in the early phase of the disease [9].

In this chapter we will provide reasons to further elucidate the complexity of COPD and heart failure and give direction for further research. Moreover, we want to provide clinicians with the tools to further improve everyday clinical management of patients with COPD, hopefully paying more attention to (non-overt) cardiovascular diseases in these patients.

History

Until 2003, heart failure was considered uncommon in patients with COPD and, whenever present, would occur as right-sided heart failure with elevated right arterial pressures, *i.e.* cor pulmonale [10]. Importantly, however, this view was based on studies performed in the 1970s, with small samples of rather young patients (mean age 53–68 years) who mostly had severe COPD and selectively no coronary artery disease (CAD) [11]. In this selected population of COPD patients, left ventricular dysfunction (left ventricular ejection fraction (LVEF) <40–50%) was relatively uncommon with prevalence rates of only 0–16% [11]. A hint that left ventricular dysfunction was much more common in unselected patients with COPD (*i.e.* without excluding patients with CAD) came from five studies published between 1975 and 1984, reporting much higher prevalence rates of left ventricular dysfunction, ranging from 10% to 46% [11]. Still, the idea that concomitant heart failure was rare in patients with COPD persisted until 2003 [11]. Then, McCULLOUGH *et al.* [12] showed that 21% of 417 patients with self-reported COPD or asthma (mean age 62 years) presenting at the emergency department with acute shortness of breath had previously unknown heart failure. In 2005, similar results were reported from a study among 405 elderly patients (mean age 73 years) with stable COPD [9]. Since then, multiple studies have addressed the occurrence of both diseases and their potential clinical consequences [3, 7, 11, 13–16], and international guidelines on both heart failure and COPD have focussed on the impact of one disease in the presence of the other [17, 18].

Definition of heart failure

Heart failure can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate proportionate to the requirements of the metabolic tissues [17]. Heart failure can also be defined clinically as a syndrome in which patients have typical symptoms (*e.g.* breathlessness, ankle swelling and fatigue) and signs (*e.g.* elevated jugular venous pressure, pulmonary crackles and displaced apex beat) resulting from an abnormality of cardiac function or structure [17]. In heart failure with reduced ejection fraction (REF), the main cardiac abnormality is left ventricular dysfunction with a reduced LVEF <40–50% [17]. In the case of heart failure with preserved ejection fraction (PEF), structural abnormalities of the heart such as left ventricular hypertrophy and left atrial enlargement and/or diastolic dysfunction can be detected with echocardiography in the presence of a LVEF >50% [17]. The main features of diastolic dysfunction on echocardiography are delayed left ventricular relaxation with ventricular stiffness and elevated filling pressures of the left ventricle [17]. For “isolated” right-sided heart

failure (cor pulmonale), symptoms and signs suggestive of heart failure are needed but, importantly, typically lack symptoms and signs of “left-sided” fluid overload, *i.e.* orthopnoea and pulmonary crackles. This occurs in the presence of a “normal” left ventricular systolic (LVEF >50%) and diastolic function, but with structural or functional abnormality of the right ventricle, resulting in a calculated systolic pulmonary artery pressure (sPAP) >50 mmHg with echocardiography [17].

However, many of the symptoms of heart failure are nonspecific and do not, therefore, help discriminate between heart failure and other problems [17]. Symptoms that are more specific (*i.e.* orthopnoea and paroxysmal nocturnal dyspnoea) are less common and are, therefore, infrequently present [17]. Many of the signs of heart failure result from sodium and water retention and are, therefore, also not specific [17]. Peripheral oedema has other causes as well, and is particularly nonspecific. Sodium and water retention resolve quickly with diuretic therapy, *i.e.* may be absent in patients receiving such treatment, as in hypertension [17]. These points highlight the need to obtain objective evidence, preferably by echocardiography, of a structural or functional cardiac abnormality that is thought to account for the patient’s symptoms and signs, in order to secure the diagnosis of heart failure. [17] Once the diagnosis of heart failure has been made it is important to establish the cause, particularly specific correctable causes, including non-cardiac causes. The precise aetiology determines whether specific treatment is needed (*e.g.* valve surgery for valvular disease) [17].

Epidemiology and pathophysiology of heart failure

Approximately 1–2% of the adult population in developed countries has heart failure with the prevalence increasing to >10% among persons aged 70 years or older [17]. There are many causes of heart failure, with CAD and hypertension being the most important [17]. About half of patients with heart failure have a low ejection fraction (<40–50%) and the other half have a PEF (>50%) [17]. Only 1% of patients with heart failure has “isolated” right-sided heart failure (cor pulmonale), with sPAP of >50 mmHg in the presence of COPD [19].

Heart failure with a PEF seems to have a different epidemiological and aetiological profile from heart failure with REF [17]. Patients with heart failure with PEF are in general older, more often female and obese, and have more concomitant cardiac and non-cardiac problems/diseases (*e.g.* chronotropic incompetence, atrial fibrillation, anaemia and diabetes) than those with REF. They are less likely to have coronary heart disease and are more likely to have hypertension than those with heart failure with REF [17]. The prognosis of those with heart failure with PEF is somewhat better than those with REF, but still poor with a 5-year mortality of all heart failure cases of around 50% [20–22]. In patients with heart failure with REF, the left ventricular systolic dysfunction starts with maladaptive changes occurring in surviving myocytes and extracellular matrix after myocardial injury (*e.g.* a myocardial infarction) leading to pathological eccentric “remodelling” of the left ventricle with dilatation and impaired contractility; one measure of which is a reduced LVEF [17]. Over time there is progressive worsening of these changes, with increasing enlargement of the left ventricle and decline in LVEF. Two mechanisms are thought to account for this progression: 1) further events leading to additional myocyte death (*e.g.* recurrent myocardial infarction); and 2) systemic responses induced by the decline in pumping function [17]. Amongst others, there are two activated key neurohumoral systems that can be targeted with drug treatment; the renin–angiotensin–aldosterone system and the sympathetic nervous system [17]. Over activation of these systems lead to further myocardial injury and detrimental systemic effects in the blood vessels, as well as the kidneys, muscles, bone marrow, liver and lungs [17]. It creates a pathophysiological “vicious circle” accounting for many of the clinical features seen in heart failure [17]. This results in episodes of frank decompensation (exacerbations) with hospital admissions and premature death, usually due to pump failure or a ventricular arrhythmia [17].

In heart failure with PEF there is typically a long-lasting low-degree of myocardial injury, *e.g.* hypertension, resulting in eventual maladaptive changes in surviving myocytes and extracellular matrix with concentric “remodelling” of the left ventricle [23]. Metabolic adaptation leads to stiffness of the myocytes and fibrotic changes of the extracellular matrix, resulting in delayed

relaxation of the left ventricle [23]. During exercise, the pressure in the left ventricle increases abruptly even with a small increase in blood volume, resulting in insufficient increase in stroke volume and thus symptoms such as breathlessness, chronic incompetence, reduced exercise tolerance and increased recovery time [23].

Systemic effects of heart failure

Ischaemic heart disease and hypertension are the main causes of heart failure and both can be considered as systemic diseases. Ischaemic heart disease develops from coronary and systemic atherosclerosis [24], a major cause of which is tobacco smoking. It leads to elevated levels of low-density lipoproteins, increases of free radicals, arterial wall hypoxia and oxidative stress, all negatively affecting the endothelial wall of the arteries [25–27]. Hypertension has multiple effects on the heart and vessels, including propagation of systemic atherosclerosis by increasing the formation of hydrogen peroxide, which has pro-inflammatory and atherosclerotic properties [26].

Systemic inflammation is another important feature of heart failure with elevated levels of cytokines and tumour necrosis factor (TNF)- α [28]. Cardiomyocytes and other cells within the myocardium can synthesise TNF- α in response to various forms of cardiac stress, including left ventricular pressure or volume overload, which is present in heart failure [29]. In the disease progression of heart failure, serum levels of the inflammatory cytokines TNF- α , interleukin (IL)-6 and C-reactive protein (CRP) are all elevated and correlated with progression of heart failure, worsening functional condition and poorer survival. To date, treatment of systemic inflammation is uncertain and anti-TNF- α treatment does not result in improved prognosis in heart failure.

Pulmonary effects of heart failure

Probably the most important pulmonary effect of heart failure is (periods of) increased pulmonary capillary wedge pressure and pulmonary congestion with interstitial and peri-bronchiolar oedema. This can result in a decrease of diffusion capacity and induction of pulmonary vascular bed “remodelling” resulting in pulmonary arteriolar wall hypertrophy [30, 31]. In addition, an increase in PAP can develop secondary to left-sided heart failure.

Acute cardiac decompensations may result in pulmonary obstruction (asthma cardiale) with wheezing and extended expirium on physical examination, which are often difficult to distinguish from asthma attacks.

Effect of heart failure on pulmonary function testing

A reduction of about 20% compared to age-, sex- and height-matched controls in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) can be expected to be caused by heart failure [32]. Fortunately, FEV₁ and FVC are affected at an almost similar degree, at least in stabilised patients who are not fluid overloaded. Thus, when in a stable phase of the disease, the FEV₁/FVC ratio is not significantly affected in the presence of heart failure [32]. However, the severity of pulmonary obstruction can be over-rated in patients with COPD in the presence of heart failure, because part of the reduction in FEV₁ % predicted is caused by heart failure [32]. As already mentioned previously, pulmonary diffusion capacity is lower in the presence of heart failure, more clearly so when patients have signs of water and salt retention on physical examination.

Systemic and cardiovascular effects of COPD

In COPD the most obvious abnormality is the “fixed” airflow limitation. Importantly, however, this airflow limitation is associated with an abnormal pulmonary and systemic inflammatory response of the lungs to tobacco smoking [3]. Other systemic effects in COPD that are at least partly related to inflammation are (periods of) hypoxaemia, oxidative stress, chronic progressive muscle

wasting and increased sympathetic tone. Systemic inflammation negatively affects the endothelial wall of (coronary) arteries, promoting atherosclerotic disease progression. Persistent systemic inflammation is associated with poor clinical outcomes in COPD [33, 34]. Inflammatory markers can be detected irrespective of smoking status and disease stage of COPD [8, 35]. To date, it is unclear whether this is due to spill-over of inflammation from the lungs into the blood, or activation of inflammatory cells in their transit through the pulmonary circulation [36]. The atherosclerotic process is further amplified by pro-inflammatory cytokines, such as TNF- α and IL-8, which are essential elements in the “cytokine cascade” as they produce increased levels of CRP [37]. In a self-perpetuating way, CRP can even up-regulate production of other inflammatory cytokines and foster leukocyte adhesion to vascular endothelium. In addition, CRP itself may be deposited directly into the arterial wall during atherogenesis [4, 7]. Moreover, neutrophils play a destabilising role in atherosclerotic plaques which may result in their rupture [8]. Thus, the systemic inflammation present in COPD is strongly related to systemic atherosclerosis [38]. This is underlined by epidemiologic studies showing that patients with COPD have an increased incidence of systemic atherosclerosis, independent of age, smoking or other cardiovascular risk factors [4, 5]. As a result, cardiovascular morbidity is common in patients with COPD [38, 39].

Momentarily, it is unknown whether systemic atherosclerosis is just an epiphenomenon associated with COPD or whether it can further induce disease progression of COPD.

In patients with COPD and (severe) hypoxaemia, other pathways can affect cardiac function more directly. Alveolar hypoxia and pulmonary vasoconstriction can lead to “remodelling” of the pulmonary vascular bed by: 1) diversion of blood flow from areas of regional alveolar hypoxia to better ventilated areas of the lung; 2) media hypertrophy of muscular pulmonary arteries; and 3) proliferation of vascular smooth muscle cells into the normally non-muscular vessels of the pulmonary circulation [40]. When extensive parts of the lungs are involved this results in pulmonary arterial hypertension and increased pulmonary vascular resistance, thus, resulting in increased workload for the right ventricle in particular, which can result in dilatation and hypertrophy of the right ventricle and eventually right-sided heart failure (*i.e.* cor pulmonale) (table 1) [41, 42].

Heart failure in COPD

Common pathophysiological pathways

Apart from the systemic effects of smoking and inflammation, there are other common pathways in COPD and heart failure that cause mutual disease progression. In both diseases, the renin-angiotensin system (RAS) is over-activated [17, 43]. Importantly, the RAS is not only active in the systemic circulation but also in organ tissue, including the lungs [43, 44]. Angiotensin-II is a potent pulmonary airway constrictor, has mitogenic effect on lung fibroblasts and can cause apoptosis of lung epithelial cells [45]. In addition, increased levels of angiotensin-II in the lungs have been related to a decrease in alveolar membrane gas exchange and an increase in both pulmonary inflammation and pulmonary vascular constriction [44–47].

The other well-established pathway in the disease progression of heart failure is sympathetic over-activity, causing systemic and direct cardiac effects [17]. It results in downregulation and reduction of the density of β_1 -adrenoreceptors in the myocardium [48]. Sympathetic over-activity can lead to increased heart rates with (short-term) increased contractility and vasoconstriction by activation of the RAS and direct cardiotoxicity with myocyte apoptosis and focal myocardial necrosis [49]. Persistence of the sympathetic over-activity of the heart and vessels and the direct negative myocardial effects lead to fluid retention and increased left ventricular wall stress. In the long run, these changes lead to overloading of the myocytes resulting in overcompensated myocardial hypertrophy, decreased myocardial contractility and eventually myocardial damage [49] and, thus, in a decrease of ventricular function, especially of the dominant left ventricle resulting in heart failure. As a result, β_1 -selective, but also non-selective β -adrenoreceptor, blockers are now established evidence-based counteracting drugs in heart failure treatment [17].

Table 1. Pathophysiological changes in COPD that can have an effect on cardiac function

	Pulmonary changes in COPD	Resulting pulmonary and systemic changes	Cardiac effects
A	Positive end-expiratory pressure increase	Venous blood return decrease	Reduced right and left ventricle preload
B	Systemic vasodilatation	Venous blood return decrease	Reduced right and left ventricle preload
C	Thoracic pressure increase, respiratory effort increase, hypoxia and hypercapnia	Generalised sympathetic over activity and eventually downregulation and density decrease of cardiac β_1 -adrenoreceptors	Increased heart rate and short-term contractility, vasoconstriction, renin-angiotensin system increase, cardiotoxicity eventually leading to myocardial hypertrophy and damage, and decreased contractility
D	Hyperinflation and increased lung volume	Pulmonary capillary wall stress increase and capillary leakage	High-permeability pulmonary oedema decreased diffusion capacity resulting in hypoxaemia (see pathways E, F and G)
E	Hypoxaemia	Myocyte hypoxia	Impaired relaxation and contraction of right and left ventricle
F	Hypoxaemia	Polycythaemia leading to serum viscosity increase and pulmonary thromboembolism	Right ventricle dilatation and hypertrophy due to increased right ventricle workload, resulting in “isolated right ventricular failure” and/or left ventricular dysfunction by diastolic flattening of the intraventricular septum
G	Hypoxaemia induces hypoxic pulmonary vasoconstriction and pulmonary vascular bed “remodelling”	Pulmonary hypertension and pulmonary vascular resistance increase	Right ventricle dilatation and hypertrophy due to increased right ventricle workload resulting in “isolated right ventricular failure” and/or left ventricular dysfunction by diastolic flattening of the intraventricular septum

In COPD, the nervous system, mainly the parasympathetic system, is also over-activated [18, 43]. However, at least in more severe COPD, several processes can also induce (ortho-) sympathetic over-activity [43]. Such processes include increased thoracic pressures, increased respiratory effort, hypoxaemia and hypercapnia [48]. The exact role of (ortho-) sympathetic over-activity in COPD is still unclear [43].

At a late stage in the disease progression of both COPD and heart failure, there is another important common mechanism. Both diseases share the same type of metabolic modulation with the cellular metabolism shifting from glucose to lipid metabolism, resulting in generalised muscle dysfunction and, eventually, chronic wasting and cachexia in the end stage of both diseases [50–52].

Diagnostic considerations

In any patient with shortness of breath, heart failure should be considered, as well as in patients with known COPD. Importantly, signs and symptoms and additional investigations, such as natriuretic peptide measurements, ECG and chest radiographs, are more difficult to interpret in patients with COPD. Key symptoms of heart failure are breathlessness, ankle swelling and fatigue [17], another common feature in patients with COPD, certainly in the elderly, is chronic venous insufficiency of the legs. Even the more typical symptoms of heart failure, *i.e.* paroxysmal nocturnal dyspnoea and orthopnoea can also be present in COPD. Other overlapping symptoms between heart failure and COPD are nocturnal cough, wheezing and loss of appetite [17]. Key signs of heart failure are an elevated jugular venous pressure, peripheral oedema and pulmonary crepitations; however, these are all related to fluid retention, a laterally displaced apical impulse and a cardiac murmur, respectively [17]. Importantly, signs of fluid retention can be absent,

especially in patients who use diuretics and in early stages of heart failure with PEF [17]. Additional investigations to increase the likelihood of heart failure include electrocardiography, serum measurements of natriuretic peptides and chest radiographs [17]. A completely normal electrocardiogram in patients with COPD makes heart failure unlikely [17, 53]. However, there are no “typical” ECG abnormalities for heart failure [17]. In addition, a B-type natriuretic value below the exclusionary cut-off point of $125 \text{ pg}\cdot\text{mL}^{-1}$ for N-terminal pro-brain natriuretic peptide (NT-proBNP) and $35 \text{ pg}\cdot\text{mL}^{-1}$ for brain natriuretic peptide (BNP) in the nonacute setting makes heart failure unlikely [17]. The same holds true for patients with COPD [53], although patients with severe COPD and pulmonary arterial hypertension have, in general, elevated levels of natriuretic peptides reaching above the aforementioned exclusion cut-off points, and higher cut-off points could be used with similar good exclusionary capacity [17]. In the acute setting, when assessing patients with acute breathlessness, higher exclusion cut-off points of natriuretic peptides should be used; $300 \text{ pg}\cdot\text{mL}^{-1}$ for NT-proBNP and $100 \text{ pg}\cdot\text{mL}^{-1}$ for BNP [17]. A chest radiograph is, generally speaking, not very useful in the diagnostic assessment of heart failure in either setting, certainly not in patients with COPD, risking misinterpretation of abnormalities and underestimation of the cardiothoracic ratio [11]. In conclusion, signs and symptoms, together with natriuretic peptide measurements, ECG and chest radiographs, can only increase (or reduce) the likelihood of heart failure, irrespective of the presence or absence of COPD. Echocardiography is the cornerstone investigation and is necessary in order to confirm the diagnosis of heart failure. In general, high-quality echocardiographic images can be made in the vast majority of COPD patients [53]. Cardiovascular magnetic resonance imaging is an alternative to echocardiography in patients with unclear views due to COPD [17].

To date, only one study has developed a prediction model to detect (or exclude) heart failure in patients with COPD [53]. The model was derived from patients with a diagnosis of COPD, aged 65 years and older, and in a stable phase of their disease [53]. Independent predictors of heart failure were: 1) a history of ischaemic heart disease (prior myocardial infarction, angina pectoris, coronary bypass grafting and percutaneous coronary intervention); 2) obesity (body mass index (BMI) $>30 \text{ kg}\cdot\text{m}^{-2}$); 3) a laterally displaced or broadened/sustained apex beat; 4) a heart rate $>90 \text{ beats}\cdot\text{minute}^{-1}$; 5) an NT-proBNP level $>125 \text{ pg}\cdot\text{mL}^{-1}$ ($\sim 15 \text{ pmol}\cdot\text{L}^{-1}$); and 6) an abnormal electrocardiogram [53]. Combining these variables in a clinical decision rule, the points for the aforementioned items were 2, 3, 3, 2, 4 and 3, respectively. With a score of 0, the risk of heart failure was 5%. With a score of 2 to 5, the risk was 24%, and for scores 6–9 and 10–14, the risk of heart failure was 35% and 57%, respectively.

Importantly, however, this model needs external validation in another cohort of COPD patients before it can be applied in everyday clinical practice.

Prognosis of heart failure in COPD

Newly detected heart failure in community-dwelling elderly patients with COPD doubles the mortality rates (25.6% *versus* 12.1%, $p=0.002$ during mean $\pm$ SD 4.2 ± 1.4 years follow-up), also independent of other factors [54]. Also, in newly diagnosed hospitalised heart failure patients, those with COPD had higher all-cause 5-year mortality compared to those without COPD [55]. Although not extensively investigated, there seems to be no significant difference in prognosis between heart failure with REF and PEF patients with coexisting COPD [56].

Pharmacological treatment considerations

Therapy of heart failure in patients with COPD is in principle the same as in those without COPD, including cardioselective β -blockers [18]. For patients truly intolerant to β -blockers, ivabradine (when heart rate is $>70 \text{ beats}\cdot\text{minute}^{-1}$) or digoxin can be considered to reduce the risk of heart failure hospitalisation (fig. 1) [17].

Diuretics relieve breathlessness and oedema in heart failure patients with signs and symptoms of congestion, irrespective of ejection fraction, but the effect of diuretics on mortality and morbidity is unclear [17]. In heart failure with REF patients, angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers (ARBs) when intolerated), β -blockers and mineralocorticoid/aldosterone receptor antagonists are all evidence-based morbidity and mortality reducing drugs and should, when possible, be prescribed and up-titrated in any patients with heart failure with REF [17]. For patients with heart failure with PEF, no treatment has yet been shown to convincingly reduce morbidity and mortality [17]. Diuretics are used in heart failure with PEF to control sodium and water retention. Adequate treatment of hypertension and myocardial ischaemia is also considered important, as is control of ventricular rate in heart failure with PEF patients with atrial fibrillation [17]. Importantly, statins are not effective in heart failure with REF [57, 58], and whether they are effective in heart failure with PEF needs to be further studied [59].

Nowadays, digoxin and other digitalis glycosides are infrequently used in heart failure with the exception of patients with concurrent atrial

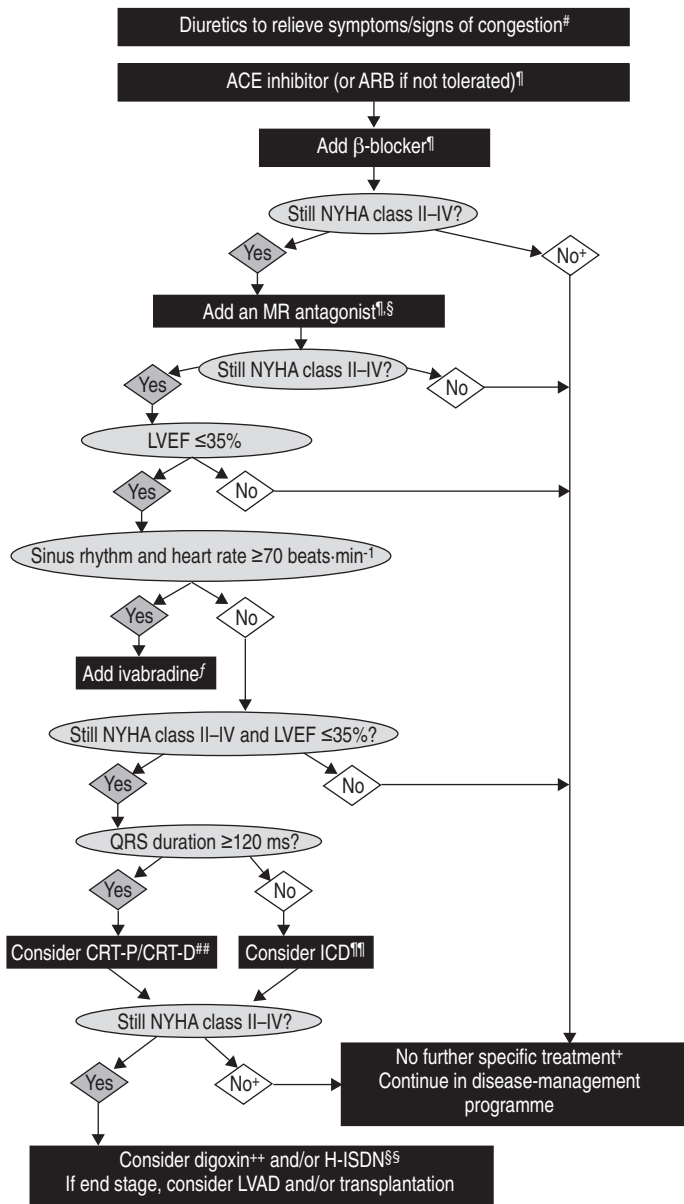


Figure 1. Treatment options for patients with chronic symptomatic heart failure (New York Heart Association (NYHA) class II-IV) and reduced ejection fraction irrespective of presence of COPD. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; MR: mineralocorticoid receptor; LVEF: left ventricular ejection fraction; CRT-P: cardiac resynchronisation therapy-pacemaker; CRT-D: cardiac resynchronisation therapy-defibrillator; ICD: implantable cardioverter-defibrillator; H-ISDN: hydralazine and isosorbide dinitrate; LVAD: left ventricular assistant device. [#]: diuretics may be used as needed to relieve the signs and symptoms of congestion but they have not been shown to reduce hospitalisation or death; [¶]: should be titrated to evidence-based dose or maximum tolerated dose below the evidence-based dose; ⁺: asymptomatic patients with an LVEF $\leq 35\%$ and a history of myocardial infarction should be considered for an ICD; [§]: if MR antagonist not tolerated an ARB may be added to an ACE inhibitor as an alternative; ^f: European Medicines Agency has approved ivabradine for use in patients with a heart rate ≥ 75 beats per minute, may also be considered in patients with a contraindication to a β -blocker or β -blocker intolerance; ^{##}: indication differs according to heart rhythm, NYHA class, QRS duration, QRS morphology and LVEF; ^{¶¶}: not indicated in NYHA class IV; ⁺⁺: digoxin may be used earlier to control the ventricular rate in patients with atrial fibrillation, usually in conjunction with a β -blocker; ^{§§}: the combination of hydralazine and isosorbide dinitrate may also be considered earlier in patients unable to tolerate an ACE inhibitor or an ARB. Reproduced from [17] with permission from the publisher.

fibrillation [17]. For more information refer to the therapeutic flow chart of the recent European Society of Cardiology guidelines on heart failure [17].

Cardiovascular drugs and their pulmonary implications in patients with COPD

β-blockers

Patients with heart failure and COPD should not be denied cardioselective β-blockers (e.g. metoprolol succinate, bisoprolol and nebivolol), although low-dose initiation and gradual up-titration (“start low, go slow”) seems even more important than in heart failure patients without COPD [14, 60]. For heart failure patients with more severe COPD the efficacy of β-blockade has not been extensively studied [14].

Nonselective β-blockers are not recommended because of the higher risk of bronchospasm, especially in the initial phase, although scarce data suggest that carvedilol (also α-blocking activity) can be used safely [14]. It is well-known that β-blockers initially have negative inotropic effects, while over time gradually displaying their cardiovascular beneficial effects. This also seems to occur in heart failure patients with COPD [14].

In a *post hoc* analysis of participants in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) programme, HAWKINS *et al.* [61] showed that β-blockers seem to be capable of counter-balancing possible negative effects of bronchodilators, including β-agonists on survival, although, the authors were not able to adjust for the severity of COPD.

Considering “always” continuing β-blockers in patients with heart failure and COPD is also underpinned by the potential beneficial pulmonary effects of long-term β-blocker use, based on animal models. Long-term use of β-blockers can upregulate β₂-receptors in the lungs and, thus, reduce the need for β-agonists and reduce inflammation [62, 63].

Interestingly, recent large observational studies provide some evidence that long-term use of cardioselective β-blockers, in particular, may reduce mortality rates and the risk of pulmonary exacerbations in patients with COPD, even in the subgroup of patients who are not known to have cardiovascular disease, and irrespective of the use of β-agonist inhalers [64–66]. Residual confounding in these studies could dilute beneficial effect of β-blockers, because β-blockers are typically prescribed to patients with increased mortality risks (*i.e.* with hypertension and cardiovascular disease). However, confounding by contraindication threatens the validity of the aforementioned observational pharmaco-epidemiological studies because β-blockers could knowingly be withheld by a clinician in patients with more severe COPD due to concerns that the drug may worsen the patient’s condition [66]. Clinicians may reserve prescription of β-blockers to those with a less severe form of COPD who may have a lower risk of mortality. This can result in confounding by contra-indication and therefore overestimation of the effect of β-blockers [66].

ACE inhibitors or ARBs

ACE inhibitors and ARBs may improve pulmonary obstruction by decreasing angiotensin-II levels [43–46]. Moreover, ACE inhibitors can also ameliorate the alveolar membrane gas exchange and decrease pulmonary inflammation and pulmonary vascular constriction [44].

A single, small randomised controlled trial (RCT) evaluated angiotensin-II blockers in patients with COPD and without obvious cardiovascular disease, evaluating surrogate end-points after 4 months of follow-up. This study showed that treatment with irbesartan resulted in an increase in total lung capacity (TLC) [67].

Two recently published observational studies showed potential benefit of ACE inhibitors for patients with COPD [68, 69]; however, these results should be interpreted cautiously, as with the observational data with (cardioselective) β-blockers and statins because of the risk of confounding.

Mineralocorticoid/aldosterone receptor antagonists: spironolactone and eplerenone

There is a lack of studies evaluating the pulmonary effects of these drugs. Importantly, they also have some angiotensin-II blocking effects. These drugs seem to improve pulmonary gas diffusion and exercise capacity in patients with heart failure [70].

Diuretics

High dosages of diuretics can cause acid–base disturbances (metabolic alkalosis) in patients with COPD and this may blunt the respiratory drive, but at normal dosages pulmonary function is not affected by diuretics [46]. Acute exacerbations of COPD can go along with water and salt retention and (intravenous) loop diuretics could possibly have a beneficial role as one of the initial treatments, reducing the left ventricular cardiac wall stress and, as a result, lower the elevated levels of natriuretic peptides [71].

Digoxin

Digitalis glycosides may reduce lung function by pulmonary vasoconstriction [46].

Statins

In addition to their cholesterol-lowering ability, statins have been shown to have pleiotropic anti-inflammatory and immune modulatory effects. Statins may be able to reduce neutrophil numbers, reduce T-cell activation and differentiation, increase apoptosis of eosinophils and regulate inflammation by enhancing phagocytosis of apoptotic cells [72, 73]. Animal studies have shown that statins inhibit the progression of emphysema in both murine and rat models [74]. Observational data show a reduction in rate of decline in FEV₁ and FVC and, thus, suggest that statins directly exert a protective effect on the pulmonary system and abrogate the adverse effects of smoking on lung function, even in those who no longer smoke [75, 76]. Multiple observational studies in human populations show a reduction in frequency of COPD exacerbations, hospitalisations and all-cause mortality by statin therapy [77]. Whether the beneficial effects of statins in COPD patients are due to pulmonary, systemic or cardiovascular effects, or a combination of the three, remains unclear [77]. Despite the encouraging results, randomised interventional trials are needed with clinical relevant outcomes, such as lung function, number of exacerbations and hospitalisations, and mortality [77].

Pulmonary drugs and their potential cardiovascular implications

β₂-agonists

For β₂-agonists, short- and long-term effects may differ [14]; especially for orally administered β-agonists in patients with heart failure who have demonstrated acute haemodynamic improvements with an increase in LVEF and cardiac index, a decrease in pulmonary wedge pressure and even an improvement in symptoms and exercise tolerance [14]. In the longer term, however, β-agonists exert numerous unfavourable cardiovascular effects that are possibly even more pronounced when prescribed orally and in patients with heart failure because of the increased chronotropic and inotropic responsiveness and vulnerability to arrhythmias of the failing myocardium to β-agonists [14]. These negative effects include tachycardia and disturbed autonomic modulation with depressed heart rate variability and, in susceptible patients, could exert ischaemic events [14]. Importantly, standard metered-dose β-agonist inhalers produce only minor systemic and biochemical abnormalities [14]. Although, observational studies reported that β-agonist inhalers in patients with heart failure and COPD may increase mortality and heart failure hospitalisations [16], adjustment for confounders showed that purported adverse effects of β-agonists may be attributable to underlying pulmonary disease [14]. RCTs have established the safety of inhalation of long-acting β-agonists in patients with COPD; however, concerns remain regarding the safety of these drugs in patients with asthma [14, 78].

Inhaled anti-cholinergics

The long-acting anti-cholinergic bronchodilator tiotropium is as equally effective as the long-acting β-agonist salmeterol, and has reassuring cardiovascular safety data [14, 79, 80]. Potentially,

anti-cholinergics can reduce acetylcholine release over a short period and thus, potentially exert adverse cardiac effects conform atropine, such as atrial and ventricular tachycardias [81]. Until now, such negative cardiac effects have not been shown [80, 81].

Inhaled and oral corticosteroids

Oral corticosteroids cause sodium and water retention, potentially leading to worsening of heart failure [17]. This effect can be expected with long-term use and, in general, does not occur with pulsed-dosing for 7–10 days. Inhaled corticosteroids have not yet shown any cardiovascular problems [17].

Nonpharmacological treatment of heart failure and COPD

Aerobic exercise training is evidence-based treatment in both COPD and heart failure [17, 18], with a large overlap in training programmes [51]. Smoking cessation should also be considered in patients with either or both diseases [17, 18].

Devices such as cardiac resynchronisation therapy or an implantable cardioverter defibrillator could be implanted in patients with heart failure with REF when needed, irrespective of the presence or absence of COPD [17].

Conclusions

Heart failure and COPD are very common, especially in the elderly. Tobacco smoking is a strong common risk factor. Both diseases are chronic and progressive and share important pathophysiological pathways, notably, systemic inflammation, activation of the neurohumoral system and metabolic modulation. In heart failure and the presence of COPD the left ventricle is mainly affected. In only approximately 1% of all heart failure cases, the right ventricle is the main cause of heart failure (cor pulmonale). Physicians should think of the possibility of heart failure in any patient with shortness of breath and fatigue, irrespective of the presence of COPD. Detecting heart failure has a major impact on prognosis and treatment. Diagnosing heart failure in patients with COPD is difficult because of the common cardinal symptoms of breathlessness and fatigue, and the difficulty of distinguishing certain signs (*i.e.* abnormal pulmonary breathing sounds). Elevated natriuretic peptides help to select those who need echocardiography to definitely establish or reject the diagnosis of heart failure. In COPD patients aged 65 years and over who are overweight with a history of ischaemic disease, a pulse rate above 90 beats·minute⁻¹ and a laterally displaced or broadened/sustained apex beat, or any combination of these clinical items, physicians should consider concurrent presence of heart failure.

A dual diagnosis of COPD and heart failure means an increase in burden of care with complex polypharmacy and the risk of miscommunication between multiple care providers. Cardiovascular drugs focused on atherosclerosis and neurohumoral over-activation could become new treatment options in COPD. The time has come where physicians should not withhold cardioselective β -blockers in patients with COPD who need these drugs for any comorbid condition. Future randomised trials could possibly confirm the long-term beneficial effects of cardiovascular drugs, notably β -blockers and statins, as seen in patients with COPD in observational pharmaco-epidemiological studies. A positive result on clinically important end-points of cardiovascular drugs in patients with COPD in such an RCT would cause a major paradigm shift in the treatment of COPD.

Statement of Interest

F.H. Rutten has received assays of N-terminal brain natriuretic peptides at a reduced price from Roche Diagnostics for a diagnostic study in patients with breathlessness.

References

1. Pedersen F, Mehlsen J, Raymond I, *et al.* Evaluation of dyspnoea in a sample of elderly subjects recruited from general practice. *Int J Clin Pract* 2007; 61: 1481–1491.

2. Mulrow CD, Lucey CR, Farnett LE. Discriminating causes of dyspnea through clinical examination. *J Gen Intern Med* 1993; 8: 383–392.
3. Fabbri LM, Luppi F, Beghé B, *et al.* Complex chronic comorbidities of COPD. *Eur Respir J* 2008; 31: 204–212.
4. Ebi K, Hawthorne VM, Rose G, *et al.* Breathlessness, chronic bronchitis and reduced pulmonary function as predictors of cardiovascular disease mortality among men in England, Scotland and the United States. *Int J Epidemiol* 1989; 18: 84–88.
5. Hole DJ, Watt GC, Davey S, *et al.* Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *Br Med J* 1996; 313: 711–715.
6. Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. *COPD* 2010; 7: 375–382.
7. Sin DD, Anthonisen NR, Soriano JB, *et al.* Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; 28: 1245–1257.
8. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; 107: 1514–1519.
9. Rutten FH, Cramer MJ, Grobbee DE, *et al.* Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005; 26: 1887–1894.
10. Kachel R. Left ventricular function in chronic obstructive pulmonary disease. *Chest* 1978; 74: 286–290.
11. Rutten FH, Cramer MJM, Lammers JWJ, *et al.* Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail* 2006; 8: 706–711.
12. McCullough PA, Hollander JE, Nowak RM, *et al.* Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003; 10: 198–204.
13. Hawkins NM, Petrie MC, Jhund PS, *et al.* Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009; 11: 130–139.
14. Hawkins NM, Petrie MC, Macdonald MR, *et al.* Heart failure and chronic obstructive pulmonary disease. The quandary of β -blockers and β -agonists. *J Am Coll Cardiol* 2011; 57: 2127–2138.
15. Mentz RJ, Fiuzat M, Kraft M, *et al.* Bronchodilators in heart failure patients with COPD: is it time for a clinical trial? *J Card Fail* 2012; 18: 413–422.
16. Au DH, Udris EM, Fan VS, *et al.* Risk of mortality and heart failure exacerbations associated with inhaled β -adrenoreceptor agonists among patients with known left ventricular dysfunction. *Chest* 2003; 123: 1964–1969.
17. McMurray JJ, Adamopoulos S, Anker SD, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012; 33: 1787–1847.
18. Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2011. www.goldcopd.org Date last accessed: September 4, 2012.
19. Naeije R. Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 20–22.
20. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012; 33: 1750–1757.
21. van Jaarsveld CH, Ranchor AV, Kempen GI, *et al.* Epidemiology of heart failure in a community-based study of subjects aged ≥ 57 years: incidence and long-term survival. *Eur J Heart Fail* 2006; 8: 23–30.
22. Steinberg BA, Zhao X, Heidenreich PA, *et al.* Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012; 126: 65–75.
23. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011; 32: 670–679.
24. Agmon Y, Khandheria BK, Meissner I, *et al.* C-reactive protein and atherosclerosis of the thoracic aorta: a population-based transesophageal echocardiographic study. *Arch Intern Med* 2004; 164: 1781–1787.
25. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 2004; 43: 1731–1737.
26. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115–126.
27. Simanionok JP. Non-ischemic hypoxia of the arterial wall is a primary cause of atherosclerosis. *Med Hypotheses* 1996; 46: 155–161.
28. Vasan RS, Sullivan LM, Roubenoff R, *et al.* Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003; 107: 1486–1491.
29. Murray DR, Freeman GL. Proinflammatory cytokines: predictors of a failing heart? *Circulation* 2003; 107: 1460–1462.
30. Assayag P, Benamer H, Aubry P, *et al.* Alteration of the alveolar-capillary membrane diffusing capacity in chronic left heart disease. *Am J Cardiol* 1998; 82: 459–464.
31. West JB, Mathieu C. Stress failure of pulmonary capillaries: role in lung and heart disease. *Lancet* 1992; 340: 762–767.
32. Gueder G, Rutten FH, Brenner S, *et al.* The impact of heart failure on the classification of COPD severity. *J Card Fail* 2012; 18: 637–644.
33. Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet* 1994; 344: 793–795.

34. Agustí A, Edwards LD, Rennard SI, *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7: e37483.
35. Oudijk E-JD, Lammers J-WJ, Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: Suppl. 46, 5s–13s.
36. MacNee W. Pathogenesis of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 258–266.
37. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685–1695.
38. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; 33: 1165–1185.
39. Lange P, Mogelvang R, Marott JL, *et al.* Cardiovascular morbidity in COPD: a study of the general population. *COPD* 2010; 7: 5–10.
40. Klinger JR, Hill NS. Right ventricular dysfunction in chronic obstructive pulmonary disease. Evaluation and management. *Chest* 1991; 99: 715–723.
41. Burghuber O, Bergmann H, Silberbauer K, *et al.* Right ventricular performance in chronic air flow obstruction. *Respiration* 1984; 45: 124–130.
42. Morrison DA, Adcock K, Collins CM, *et al.* Right ventricular dysfunction and the exercise limitation of chronic obstructive pulmonary disease. *J Am Coll Cardiol* 1987; 9: 1219–1229.
43. Andreas S, Anker SD, Scanlon PD, *et al.* Neurohormonal activation as a link to systemic manifestations of chronic obstructive pulmonary disease. *Chest* 2005; 128: 3618–3624.
44. Forth R, Montgomery H. ACE in COPD: a therapeutic target? *Thorax* 2003; 58: 556–558.
45. Mancini GB, Khalil N. Angiotensin II type 1 receptor blocker inhibits pulmonary injury. *Clin Invest Med* 2005; 28: 118–126.
46. Aronow WS. Treatment of heart failure in older persons. Dilemmas with coexisting conditions: diabetes mellitus, chronic obstructive pulmonary disease, and arthritis. *Congest Heart Fail* 2003; 9: 142–147.
47. Guazzi M. Alveolar-capillary membrane dysfunction in heart failure: evidence of a pathophysiologic role. *Chest* 2003; 124: 1090–1102.
48. Sakamaki F, Satoh T, Nagaya N, *et al.* Abnormality of left ventricular sympathetic nervous function assessed by ¹²³I-metaiodobenzylguanidine imaging in patients with COPD. *Chest* 1999; 116: 1575–1581.
49. Jackson G, Gibbs CR, Davies MK, *et al.* ABC of heart failure. Pathophysiology. *Br Med J* 2000; 320: 167–170.
50. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation* 2005; 111: 2837–2849.
51. Gosker HR, Lencer NH, Franssen FM, *et al.* Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest* 2003; 123: 1416–1424.
52. Schols AM. Nutritional and metabolic modulation in chronic obstructive pulmonary disease management. *Eur Respir J* 2003; 22: Suppl. 46, 81s–86s.
53. Rutten FH, Moons KCM, Cramer MJM, *et al.* Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. *Br Med J* 2005; 331: 1379.
54. Boudestein LC, Rutten FH, Cramer MJM, *et al.* The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Failure* 2009; 11: 1182–1188.
55. Rusinaru D, Saadi I, Godard S, *et al.* Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *Am J Cardiol* 2008; 101: 353–358.
56. Kwon BJ, Kim DB, Jang SW, *et al.* Prognosis of heart failure patients with reduced and preserved ejection fraction and coexistent chronic obstructive pulmonary disease. *Eur J Heart Fail* 2010; 12: 1339–1344.
57. Kjekshus J, Apetrei E, Barrios V, *et al.* Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; 357: 2248–2261.
58. Tavazzi L, Maggioni AP, Marchioli R, *et al.* Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 1231–1239.
59. Fukata H, Sane DC, Brucks S, *et al.* Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. *Circulation* 2005; 112: 357–363.
60. Jabbour A, Macdonald PS, Keogh AM, *et al.* Differences between beta-blockers in patients with chronic obstructive pulmonary disease: a randomized crossover trial. *J Am Coll Cardiol* 2010; 55: 1780–1787.
61. Hawkins NM, Wang D, Petrie MC, *et al.* Baseline characteristics and outcomes of patients with heart failure receiving bronchodilators in the CHARM programme. *Eur J Heart Fail* 2010; 12: 557–565.
62. Lin R, Peng H, Nguyen LP, *et al.* Changes in β 2-adrenoceptor and other signaling proteins produced by chronic administration of “ β -blockers” in a murine asthma model. *Pulm Pharmacol Ther* 2008; 21: 115–124.
63. Nguyen LP, Omoluabi O, Parra S, *et al.* Chronic exposure to β -blockers attenuates inflammation and mucin content in a murine asthma model. *Am J Respir Cell Mol Biol* 2008; 38: 256–262.
64. Rutten FH, Zuithoff NPA, Hak E, *et al.* β -blockers may reduce mortality and risk of exacerbations of patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2010; 170: 880–887.
65. Short PM, Lipworth SI, Elder DH, *et al.* Effect of β -blockers in treatment of chronic obstructive pulmonary disease. *Br Med J* 2011; 342: d2549.
66. Etminan M, Jafari S, Carleton B, *et al.* β -blocker use and COPD mortality: a systematic review and meta-analysis. *BMC Pulm Med* 2012; 12: 48.

67. Andreas S, Herrmann-Lingen C, Raupach T, *et al.* Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial. *Eur Respir J* 2006; 27: 972–979.
68. Mancini GB, Etminan M, Zhang B, *et al.* Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006; 47: 2554–2560.
69. Mortensen EM, Copeland LA, Pugh MJV, *et al.* Impact of statins and ACE inhibitors on mortality after COPD exacerbations. *Resp Res* 2009; 10: 45.
70. Agostoni P, Magini A, Andreini D, *et al.* Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J* 2005; 26: 159–164.
71. Zhang J, Zhao G, Yu X, *et al.* Intravenous diuretic and vasodilator therapy reduce plasma brain natriuretic peptide levels in acute exacerbation of chronic obstructive pulmonary disease. *Respirology* 2012; 17: 715–720.
72. Walsh GM. Defective apoptotic cell clearance in asthma and COPD: a new drug target for statins? *Trends Pharmacol Sci* 2008; 29: 6–11.
73. Morimoto K, Janssen WJ, Fessler MB, *et al.* Lovastatin enhances clearance of apoptotic cells (efferocytosis) with implications for chronic obstructive pulmonary disease. *J Immunol* 2006; 176: 7657–7665.
74. Lee JH, Lee DS, Kim EK, *et al.* Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. *Am J Respir Crit Care Med* 2005; 172: 987–993.
75. Keddissi JI, Yuonis WG, Chbeir EA, *et al.* The use of statins and lung function in current and former smokers. *Chest* 2007; 132: 1764–1771.
76. Alexeeff SE, Litonjua AA, Sparrow D, *et al.* Statin use reduces decline in lung function: VA Normative Ageing Study. *Am J Respir Crit Care Med* 2007; 176: 742–747.
77. Janda S, Park K, Fitzgerald JM, *et al.* Statins in COPD. A systematic review. *Chest* 2009; 136: 734–743.
78. Calverly PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
79. Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
80. Chong J, Karner C, Poole P. Tiotropium *versus* long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 9: CD009157.
81. Casaburi R, Mahler DA, Jones PW, *et al.* A long-term evaluation of once-daily inhaled tiotropium I chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–224.

Chapter 5

Infection and comorbidity

Richa Singh, Alexander J. Mackay and Jadwiga A. Wedzicha



SUMMARY: COPD is a complex, multidimensional disease with both pulmonary and extrapulmonary comorbidities playing a significant role in the natural history of the disease. Airway infections play a pivotal part in the effects of comorbidities in patients with COPD. Infections may act either directly, worsening the underlying airway inflammation, or indirectly, amplifying the effects of comorbidities through acute exacerbations, lower airway bacterial colonisation, systemic inflammation and cardiovascular manifestations.

Patients with COPD are at a higher risk of pneumonia and have worse outcomes than patients without COPD, and the risk appears further increased by the use of inhaled corticosteroids (ICS). Similarly, the risk of atypical infections, such as non-tuberculous mycobacteria and *Aspergillus* spp., may be increased with ICS use. Repeated infections lead to a vicious circle of inflammation, with the risk of subsequent bronchiectasis. Novel treatments are urgently required to improve the far-reaching consequences of this important disease.

KEYWORDS: Atypical, cardiovascular, exacerbations, infection, inflammation, pneumonia

Centre for Respiratory Medicine,
University College London Medical
School, Royal Free Campus, London,
UK.

Correspondence: R. Singh, Centre for
Respiratory Medicine, University
College London Medical School,
Royal Free Campus, Rowland Hill
Street, London NW3 2PF, UK.
Email: r.singh@ucl.ac.uk

Eur Respir Monogr 2013; 59: 64–79.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011512
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

COPD is characterised by airflow limitation and is associated with persistent lung and systemic inflammation, which increases during episodes of acute exacerbations [1]. COPD often coexists with other important pulmonary and extrapulmonary conditions that can have a significant impact on morbidity and prognosis [2]. Infections play a pivotal role in the influence of comorbidities in patients with COPD. Infections may worsen the underlying inflammation directly and lead to comorbidities such as pneumonia, bronchiectasis and atypical infections. However, infections may also indirectly amplify the effects of comorbidities through acute exacerbations, lower airway bacterial colonisation and systemic inflammation. Acute exacerbations, characterised by a worsening of symptoms from the usual stable state, are critical events, worsening lung function decline [3, 4], increasing morbidity [5] and mortality [6], and are associated with increased airway and systemic inflammation [7, 8]. These events are likely to provide important mechanisms underpinning the relationship between COPD, infections and comorbidities, especially cardiovascular disease.

Inflammation, exacerbations and cardiovascular disease

Comorbid ischaemic heart disease is associated with worse health status, lower exercise capacity and more dyspnoea in stable patients with COPD as well as longer exacerbations [9]. COPD patients are

also at an increased risk of cardiovascular events, independently from other known cardiovascular risk factors [10–12], with approximately 30% deaths due to cardiovascular disease [13, 14].

Increased levels of systemic inflammatory markers have been directly or indirectly linked with an increased risk of thrombus formation and cardiovascular events [15–17]. Plasma fibrinogen is an independent risk factor for cardiovascular disease and is elevated in patients with symptoms of chronic bronchitis [18] and stable COPD [7]. Elevated fibrinogen has also been shown to predict higher mortality among stage 2, 3 or 4 COPD patients [19]. The symptomatic burden of stable COPD patients may also be related to fibrinogen levels. The COPD assessment test (CAT), an eight-item validated health status questionnaire, is increased at baseline in patients with frequent exacerbations and significantly linked to fibrinogen levels [20].

Plasma fibrinogen levels increase at exacerbation [7] and reduce significantly during recovery [21, 22]. The rise in fibrinogen seen at exacerbation seems to respond to corticosteroids, since treatment of exacerbations with intravenous steroid treatment leads to significantly larger reductions in fibrinogen than in patients treated with nonsteroidal drugs alone [23]. Elevated fibrinogen levels seen at exacerbation may relate to infective aetiology, since exacerbations characterised by purulent sputum, increased cough and colds have been shown to have greater rises in fibrinogen [7]. Viral exacerbations in particular are associated with higher plasma fibrinogen concentrations when compared with nonviral exacerbations [24].

Further support for the interaction between fibrinogen and infection arises from sputum studies of COPD patients, which revealed that airway bacterial colonisation is associated with higher fibrinogen levels [25]. In addition, chronic respiratory syncytial virus (RSV) infections have also been shown to be associated with increased plasma fibrinogen levels in the stable state [24]. Stable-state plasma fibrinogen levels also increase more quickly over time in frequent exacerbators compared with infrequent exacerbators and elevated plasma fibrinogen is also associated with a faster decline in lung function (fig. 1) [26].

The upregulation of inflammatory pathways and platelet activation at exacerbation may precipitate an acute cardiovascular event in COPD patients. The formation of platelet–monocyte aggregates is an early process in atherothrombosis [27] and recent data have shown that patients with stable COPD have increased circulating platelet–monocyte aggregates compared with well-matched controls [28]. Platelet activation is further increased in patients with COPD during an acute exacerbation and this mechanism may, in part, explain the increased cardiovascular risk in COPD patients [28]. Interleukin (IL)-6 increases the sensitivity of platelets to thrombin activation [29] and systemic IL-6 increases at exacerbation [7], particularly in the presence of an identifiable infective pathogen [24], suggesting that acute infection plays a large role in the increased cardiovascular risk seen in COPD patients.

There is evidence from animal models that systemic inflammation and infections accelerate atherogenesis [30], and may subsequently impart an increased cardiovascular risk. It has been shown that both influenza infections and urinary infections impart a transient, but considerable, increased risk of myocardial infarction and stroke, but no such risk occurred following common vaccinations [31, 32]. This has led to further investigation into the potential protective effects of influenza vaccination against cardiovascular events. A systematic review [33] only demonstrated one trial with beneficial effects but subsequently, a self-controlled case-series study showed a significant reduction in MI post vaccination, especially for those given early seasonal vaccinations [34]. In view of this, and the consistent association between influenza and MI, vaccination may considerably reduce the risk of vascular events.

Further evidence to support a link between acute infective exacerbations and cardiovascular disease has been provided by analysis of data from 25,857 patients with COPD in The Health Improvement Network database [35]. A 2.27-fold increased risk of MI was found 1 to 5 days after exacerbation (defined by prescription of both steroids and antibiotics) (fig. 2) and one in every 2,513 exacerbations was associated with an MI within 1–5 days. The timing of the increased cardiac risk suggests that acute infection and the consequent rise in inflammation may be playing a critical role in precipitating cardiac events.

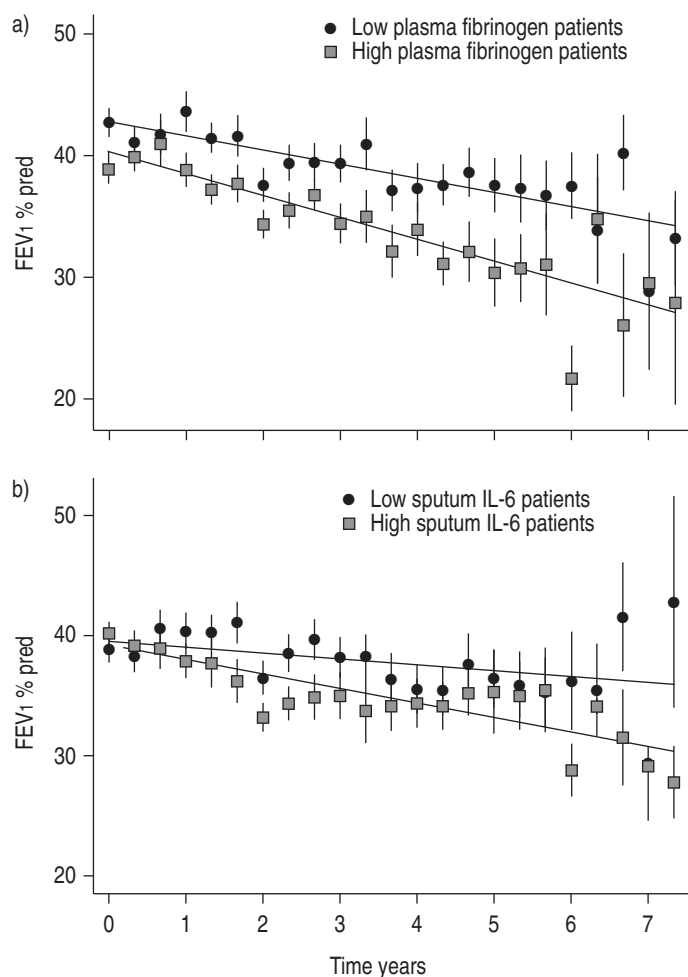


Figure 1. The mean forced expiratory volume in 1 second (FEV₁) expressed as percentage predicted (% pred) taken over a 4-month period for a) plasma fibrinogen and b) sputum interleukin (IL)-6, for each patient and plotted against the time from which each patient was recruited. The error bars are ± 2 SE and are seen to increase with time, as not all patients participated in the study for 7.33 years. No adjustment was made for covariates. Reproduced from [26] with permission from the publisher.

anti-chlamydial antibiotic roxithromycin in patients presenting acutely with acute coronary syndromes, has been reported to reduce rates of cardiac ischaemic death, MI, and severe recurrent ischaemia for at least 6 months following treatment [39]. Furthermore, in male survivors of MI, the risk of future cardiac events appeared to be related to an elevation in anti-chlamydia antibody titres and treatment with a short course of azithromycin reduced antibody titres and cardiovascular events [40].

However, whilst prophylactic macrolide antibiotics, including azithromycin, have been shown to reduce exacerbation frequency in COPD patients [41, 42], studies have shown that atypical bacteria, including *C. pneumonia*, are not major pathogens in COPD, either in the stable state or at exacerbation [43, 44]. Indeed, SEEMUNGAL *et al.* [45] found no relationship between *C. pneumoniae* immunoglobulin (Ig)G titres and lung function, exacerbation frequency, plasma fibrinogen, or serum IL-6 levels in the stable state, and no relationship between *C. pneumoniae* detection and inflammatory markers at exacerbation [45]. Thus, whilst this organism is a known cause of

Chlamydia, COPD and atherosclerosis

In addition to increased systemic inflammation, a potential mechanistic link has also been suggested between the organism *Chlamydia pneumoniae* and coronary heart disease. *C. pneumoniae* accounts for up to 10% of all cases of pneumonia and may also amplify smoking-associated inflammation in the bronchi. In this way *C. pneumoniae* has been postulated to be a contributory factor in the development of the pathological changes seen in COPD [36]. Chronic colonisation by *C. pneumoniae* is associated with lung function impairment and is more common in patients with COPD than age-matched controls [37].

Patients with chronic coronary artery disease (CAD) and following an acute MI have demonstrated elevated levels of antibodies towards *C. pneumoniae* antigens, suggesting that chronic *C. pneumoniae* infections might play a role in chronic coronary disease and that acute coronary events may be associated with acute exacerbations of chronic chlamydial disease [38].

Antibiotic studies have also suggested that targeting *C. pneumoniae* may lead to improved cardiac outcomes. Treatment with the

community-acquired pneumonia (CAP), it is highly unlikely that *C. pneumoniae* is making a major contribution to the increased cardiovascular disease associated with COPD exacerbations.

Diabetes

Diabetes is a risk factor for cardiovascular disease and appears to be an important influence on COPD exacerbations. Comorbid diabetes mellitus prolongs the length of stay and increases the risk of dying in patients hospitalised with acute exacerbations of COPD [46]. Furthermore, in COPD patients presenting with acute decompensated respiratory failure treated with noninvasive ventilation (NIV), the presentation of hyperglycaemia is associated with a poor outcome [47]. These adverse outcomes may directly be related to the acute infection and inflammation seen at exacerbation, since IL-6 has been demonstrated to be a predictor of insulin resistance [48].

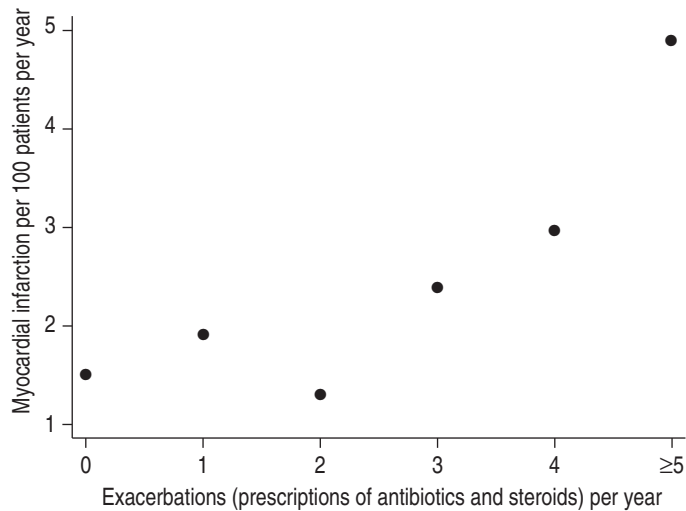


Figure 2. Annual rate of myocardial infarction against the annual rate of exacerbation defined as prescription of steroids and antibiotics together. Reproduced from [35] with permission from the publisher.

Pneumonia

CAP is the eighth leading cause of death in the USA [49] and the third leading cause of death worldwide [50]. It is difficult to determine precisely the epidemiological, clinical and socio-economic impact from CAP. Published data are limited by numerous factors including: a lack of a clear definition for CAP, nonmandatory reporting and difficulties with the identification of causative pathogens; all of which contribute to an under-reporting of CAP [51]. However, epidemiological studies have shown that COPD is one of the most common comorbidities associated with CAP [52, 53] and COPD patients are more likely to have worse clinical outcomes, contributing to the overall socioeconomic costs of CAP [51, 54].

The British Thoracic Society (BTS) defines CAP as a clinical syndrome consisting of symptoms of an acute lower respiratory tract illness (cough and at least one other lower respiratory tract symptom), new focal chest signs on examination and at least one systemic feature such as sweating, fevers or shivers, with no other explanation for the illness [55]. Many of the symptoms described for CAP overlap with those seen in COPD exacerbations. Exacerbations are often heterogeneous events, and thus difficult to define exactly. The most general clinical definition is one of a sustained worsening of a patient's condition, from stable state and beyond day-to-day variations that is acute in onset and may warrant additional treatment [56]. COPD patients may experience increased dyspnoea, increased sputum volume and purulence associated with exacerbations, and such exacerbations are often treated with antibiotics [57]. However, an exacerbation is often a diagnosis of exclusion, as other clinical conditions may cause similar symptoms, mimicking those of an exacerbation. Without radiological imaging to validate the diagnosis of pneumonia, the clinical presentation of these distinct conditions can overlap [58]. This has important implications for studies investigating pneumonia in patients with COPD. Chest radiography (or in a small number of studies computed tomography (CT)) are often only available when patients present to hospital. Thus, many studies comparing CAP in patients with or without an underlying diagnosis of COPD are performed in a hospital environment. Such patients may not represent the general population and may bias results.

COPD patients with CAP tend to have worse outcomes than non-COPD patients. In studies involving hospitalised patients with CAP, COPD patients were found to be: older; more likely to have other concomitant comorbidities, such as diabetes or chronic heart failure [59–61]; have worse clinical outcome data, such as tachypnoea or respiratory failure [59, 61]; a higher pneumonia severity index [61]; and more likely to require an intensive care unit (ICU) admission [59]; when compared with patients without COPD. In addition, the overall mortality rate was higher in patients with underlying COPD [59, 61].

In order to avoid some of the inherent bias present in studies using hospitalised patients, a recent longitudinal study was carried out in a UK-based general practice population to determine the natural history of CAP in patients with COPD [62]. The overall incidence rate of CAP was over 10-fold higher than that seen in previous primary care studies [63, 64]. As with hospital studies, age and underlying comorbidities were found to be independent risk factors for CAP, as were previous hospitalisation for an acute exacerbation of COPD and the severity of underlying disease.

Streptococcus pneumoniae is the most frequent cause of CAP and accounts for up to 40% of bacteriologically confirmed cases [55, 65, 66]. Other common pathogens include *Mycoplasma pneumoniae* and *C. pneumoniae* in up to 25% of cases. Mixed aetiologies may be found in up to 15–20% of CAP cases, and are associated with a higher mortality [66]. Patients with COPD are often chronically colonised with potentially pathogenic microorganisms (PPMs) [67–69]. In such patients, *H. influenzae* is the most common PPMs isolated [70, 71] with *Moraxella catarrhalis* also frequently cultured. Both these pathogens may be more common in COPD patients presenting with pneumonia and may potentially contribute to mixed aetiology CAP cases.

Often a causative pathogen for CAP is not identified and empirical treatment is based on the likelihood of the underlying causative pathogen. Several studies have failed to show any significant differences in pneumonia aetiology between patients with or without underlying COPD [60, 61, 72, 73]. However, both RESTREPO *et al.* [59] and PIFARRE *et al.* [60] showed more infections attributable to *P. aeruginosa* and a trend towards a higher influence of *H. influenzae*. *P. aeruginosa* is an uncommon pathogen in CAP. However, iatrogenic immunosuppression agents, such as corticosteroid therapy [74], previous hospitalisation [75] and worsening COPD disease severity [76] may increase its incidence in COPD patients.

There is limited information as to whether the clinical presentation and course of CAP is influenced by the underlying aetiological agent. One study found that bacteraemic pneumococcal pneumonia was more likely in COPD patients [77]. Surprisingly, recent studies have shown that COPD patients with bacteraemic pneumococcal pneumonia were shown to have less shock and a lower mortality rate than non-COPD patients [78] and that underlying COPD was a protective factor against pulmonary complications of pneumococcal CAP [79]. While the authors of the latter study postulated that this protective effect was due to different inflammatory responses when both CAP and COPD are present, which they had shown in previous work [80], further mechanistic and clinical studies are required to investigate this hypothesis, as this protective effect could be due to the fact that COPD patients will be more symptomatic and present earlier.

Inhaled corticosteroids and increased risk of pneumonia

Recently, large prospective studies [81–83] and meta-analyses [84, 85] have reported an increased incidence of pneumonia in patients treated with inhaled corticosteroids (ICS). However, the relationship between ICS use and pneumonia in COPD patients remains controversial.

The first reported association came from the multinational TORCH study (Towards a Revolution in COPD Health) [81], which assessed the impact of the ICS fluticasone combined with the long-acting β -agonist (LABA) salmeterol. Adverse events were reviewed at each study visit and times to pneumonia were compared, although pneumonia was not a protocol predefined, specified, secondary end-point. There was a significant reduction in the annual exacerbation frequency with the ICS/LABA combination, with a number needed to treat of four to prevent one exacerbation in

one year. However, somewhat paradoxically, the probability of having pneumonia reported as an adverse event was 19.6% in the combination group, 12.3% in the placebo group, 13.3% in the salmeterol group and 18.3% in the fluticasone group ($p < 0.001$). The study lacked a clear definition of pneumonia including radiological validation of the diagnosis, but as this finding was observed in different subgroups, the authors concluded that it was likely that such an association existed and further investigation was warranted.

A subsequent *post hoc* analysis of the TORCH data demonstrated that those pneumonias reported as both adverse events and serious adverse events were higher in groups treated with the ICS, either alone or in combination with the LABA [82]. As in the studies investigating patient characteristics in CAP [59–61], risk factors for CAP identified in the TORCH study included older patients and worsening disease severity, in addition to any COPD exacerbation in the previous year, worse medical Research Council (MRC) dyspnoea score and decreased body mass index (BMI). Less than 1% of all deaths were reported as caused by pneumonia and no differences were seen in the different treatment arms, although the study was not powered to detect such a difference.

This study highlighted the apparent paradox between a reduction in the incidence of acute exacerbations of COPD yet a rise in the pneumonias, and the problem of differentiating clinically exacerbations from pneumonias without radiology. The lack of a clear definition of pneumonia as an adverse outcome has been problematic in further studies attempting to clarify the relationship between ICS therapy and pneumonia. In an observational study of serious pneumonias in COPD patients admitted to hospital, while demonstrating a dose–response effect between ICS dose and the rate ratio of hospitalisation, cases were defined using a diagnosis database with no radiological validation [86]. In two subsequent meta-analyses, including all published randomised trials with ICS therapy, there were considerable study heterogeneity, lack of objective definitions for pneumonia, and lack of patient-level data including antibiotic usage, to control for confounding factors. As a result, the authors refrained from making a final conclusion on this relationship [84, 85].

The INSPIRE study (Investigating New Standards for Prophylaxis in Reducing Exacerbations) compared an ICS/LABA combination therapy against tiotropium and did not have *a priori* definition of pneumonia in the study protocol. However, the study physicians did review those pneumonias reported as serious adverse events to determine whether chest radiographs were used to make the diagnoses [83]. Patients completed daily symptom diary cards throughout the study, enabling accurate identification of COPD exacerbations and allowing the relationship between exacerbations and pneumonias to be investigated in more detail. The estimated on-treatment probability of pneumonia by 2 years was 9.4% in the ICS/LABA arm and 4.9% in the tiotropium arm (fig. 3) [83]. No difference in the number of *de novo* pneumonias (those not preceded by exacerbation symptoms) was seen between the different treatment groups. However, pneumonia was more likely either after a treated or untreated, unresolved exacerbation in those patients receiving ICS therapy.

In the above studies, all-cause mortality was not increased by ICS use. Some studies have demonstrated that prior ICS use improves pneumonia outcomes both as a decreased need for intensive care [87] and short-term mortality in COPD patients hospitalised with pneumonia [87, 88], suggesting that whilst COPD patients treated with ICS are at increased risk of pneumonia, the episodes are of reduced severity.

Differences exist in the pharmacological action and metabolism of ICS. Higher potency ICS therapies, such as fluticasone, are cleared more slowly from the plasma than budesonide [89]. Whether budesonide has a similar effect as that reported for fluticasone was reviewed in a meta-analysis by SIN *et al.* [90]. This meta-analysis had access to patient-level data and so was able to adjust for confounding factors that were unavailable in previous meta-analyses of fluticasone [84, 85]. In these studies, the analysis was once again limited by lack of chest radiography validation to confirm the diagnosis of pneumonia, and also by the smaller study sizes and the shorter maximum observation period. Therefore, while no increased risk of pneumonia with budesonide treatment was found, it is difficult to compare this risk with that of fluticasone.

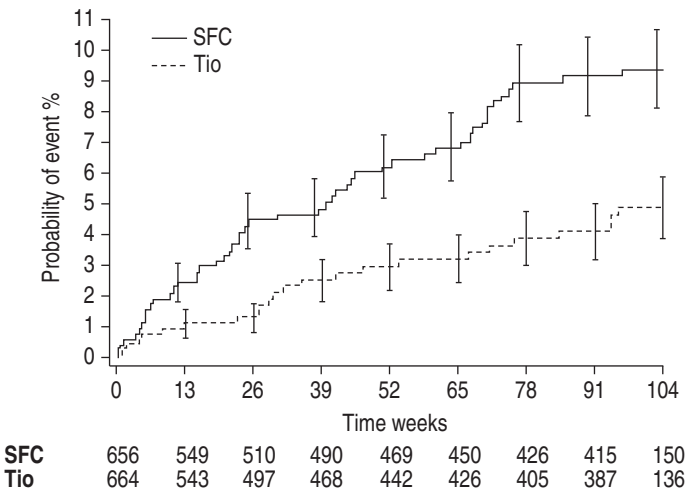


Figure 3. Time to the first incidence of pneumonia plotted against the probability of pneumonia occurring. The salmeterol/fluticasone propionate (SFC) and tiotropium (Tio) were administered at 50/500⁻¹ µg *b.i.d.* and 18 µg *q.d.*, respectively. The number of patients at risk is defined for each arm of the study underneath the graph. Reproduced from [83] with permission from the publisher.

airway bacterial colonisation in stable COPD has been shown to be a common and an important factor in the pathogenesis of COPD, increasing airway inflammation and exacerbation frequency and worsening lung function decline [70, 93, 94].

More recently, a plausible relationship between lower airway bacterial colonisation and increased susceptibility of pneumonia has been shown by GARCHA *et al.* [44]. Using molecular techniques to detect typical airway bacteria (*H. influenzae*, *S. pneumoniae* and *M. catarrhalis*) in stable COPD patients, total airway bacterial load was shown to be significantly higher with increasing ICS dose, independent of age, smoking status and disease severity (fig. 4). Furthermore, in a mouse model of pneumonia, which used a *Klebsiella pneumoniae* challenge, both airway and systemic bacterial load were higher in animals treated with 8 days of inhaled fluticasone compared with those without fluticasone [95], adding further weight to the proposal that increasing airway bacterial load may play a role in the increased risk of pneumonia with ICS therapy.

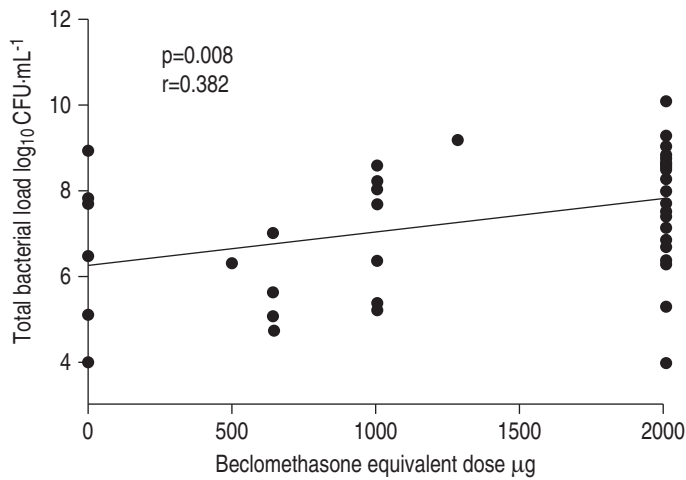


Figure 4. Relationship between the daily inhaled corticosteroid (beclomethasone) dose and total airway bacterial load. Data from [44].

The pathophysiological mechanisms, which underpin the relationship between ICS use and pneumonia, are unclear and there have been limited studies designed to investigate this relationship. Previous experimental work has shown the importance of the transcription factor nuclear factor (NF)-κB, which mediates downstream signalling pathways generating pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α and IL-6 [91], which may play an important role in the pathogenesis of COPD [92]. While ICS inhibition of NF-κB is beneficial as an anti-inflammatory response, it may also inhibit the immune response to PPMs, a potential cause for the increased incidence of pneumonia. Lower

The relationship between ICS use and increased pneumonia risk remains controversial, with conflicting evidence between studies. No published studies have been specifically designed to assess the risk of pneumonia in patients using ICS and without the use of radiology it is almost impossible to clinically differentiate between an exacerbation of COPD and pneumonia. To resolve these problems and to clarify this relationship, further large prospective and mechanistic studies are much needed. In the interim, the potential increased risk of pneumonia should be carefully balanced against the beneficial effects of

ICS therapy, and healthcare workers should remain vigilant to the possibility of developing pneumonia.

Non-tuberculous mycobacteria

Non-tuberculous mycobacteria (NTM) are a group of opportunistic mycobacteria commonly found in the environment, particularly soil and water [96]. Unlike *Mycobacterium tuberculosis*, human-to-human transmission has not been described. Infection in humans is thought to be acquired through environmental exposure, but often the source cannot be isolated [97]. NTMs are generally low-grade pathogens. Different organisms have diverse disease-producing capabilities, and may cause both asymptomatic infection and symptomatic disease (NTM lung disease; NTMLD) in those individuals with an increased susceptibility to NTM [98], with *Mycobacterium avium* complex, *Mycobacterium fortuitum* and *Mycobacterium kansasii* the most frequently reported PPMs [99].

There is limited information on the epidemiology of NTMLD. In most countries, reporting is not mandatory and the differentiation between asymptomatic infection and disease is often challenging. However, studies have suggested that the incidence has remained unchanged in developed countries over the last few years [100, 101]. NTMLD has been associated with impaired host immunity, both genetic [102] and acquired [103]. Prevalence and case series studies have shown an increased susceptibility to NTMLD with increasing age and with underlying chronic respiratory conditions which cause abnormal bronchial mucosa, including COPD [104, 105]. In one study, 27% of patients where an NTM had been isolated it was found that the patients had an underlying respiratory disorder and 46% patients fulfilled a modified American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) criteria for NTMLD [101]. Despite this, there are few population-based studies investigating the prevalence, incidence and risk factors for NTMs.

With the ongoing debate on the relationship between ICS therapy and pneumonia in COPD, the potential increased risk of NTMLD with ICS use has been suggested [106, 107]. In a recent Danish case-control study [107], population databases were used to assess the types of chronic respiratory disease and ICS therapy as risk factors for NTMLD. 42.2% of patients with chronic respiratory disease and an NTMLD had an underlying diagnosis of COPD, with an adjusted odds ratio for NTM of 7.8 (95% confidence interval 5.2–11.6). 70% of COPD patients were treated with ICS therapy (54% fluticasone and 44% budesonide). The adjusted OR for COPD with no ICS use was 7.6 (95% CI 3.4–16.8) compared to an OR of 29.1 (95% CI 10.7–73.4) in patients with COPD and current ICS use, suggesting a substantial increase in risk of an NTMLD.

The question arises as to whether this is a true reflection of risk from ICS therapy rather than reflecting the underlying COPD disease severity, when patients are more likely to be treated with an ICS. In this study, the ORs were highest for those patients on ICS after adjustment for oral steroid use and other comorbidities, suggesting the risk is independent of disease severity. In addition, over half of the patients prescribed ICS therapy had mild disease and no exacerbations in the previous year, and therefore the risk of NTM was attributed to ICS dose itself rather than to underlying disease severity. As in the ICS and pneumonia studies, the strongest association with an NTMLD and ICS use, was seen with higher ICS doses (>800 µg beclomethasone or equivalent dose).

As has been suggested by studies investigating the relationship between ICS therapy and pneumonia, clinician vigilance for symptoms of an NTMLD is recommended in COPD patients treated with an ICS, and prompt investigation with at least three early-morning sputa specimens, chest radiographs or CT is advised [99].

Bronchiectasis

In healthy individuals, the innate immune system maintains the sterility of the airways, based on traditional, culture-based techniques. However, in patients with COPD, various mechanisms of

the innate immune system, including mucociliary clearance, secretion of antimicrobial proteins and phagocytosis by both macrophages and neutrophils, are defective [71, 108]. As a result, PPMs most frequently *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, are able to persist in the lower airways. Bacterial colonisation is evident in up to 50% of sputum and bronchoscopic samples in stable COPD patients [67–70, 109] and is associated with higher airway inflammation [93] and exacerbation frequency [70]. This further worsens the underlying airway inflammation, further damaging the airway epithelial cells and thereby worsening an already defective host innate immune system, leading to a self-perpetuating cycle, known as the vicious-circle hypothesis of infection and inflammation (fig. 5) [71]. Consequently, this cycle of infection and inflammation can result in irreversibly damaged and dilated bronchi, characteristic of bronchiectasis [110].

The incidence of clinically significant bronchiectasis in COPD is unknown, as symptoms of cough and sputum production are often attributed to the underlying disease. Radiological bronchiectasis is a pathological end-point seen on high-resolution (HR)CT and may be due to several disease processes. In one study, radiological bronchiectasis was noted on 29% of CT images from primary care COPD patients [111]. With the exception of smoking history, there were no differences between patients with or without radiological bronchiectasis and the clinical implications of this finding were unclear.

The relationship between COPD and bronchiectasis was addressed in more detail by PATEL *et al.* [112]. HRCTs were performed in the well-characterised East London COPD cohort. Patients completed daily diary cards, enabling accurate symptom monitoring and calculation of exacerbation frequency, which could be related to the underlying HRCT changes. 50% of patients were found to have significant detectable bronchiectasis on HRCT and these patients had higher levels of airway inflammation than patients without significant bronchiectasis. The presence of lower lobe bronchiectasis was related to the percentage of patients colonised by a PPM (fig. 6) and was associated with a longer recovery of symptoms following an exacerbation, although was not related to exacerbation frequency [112].

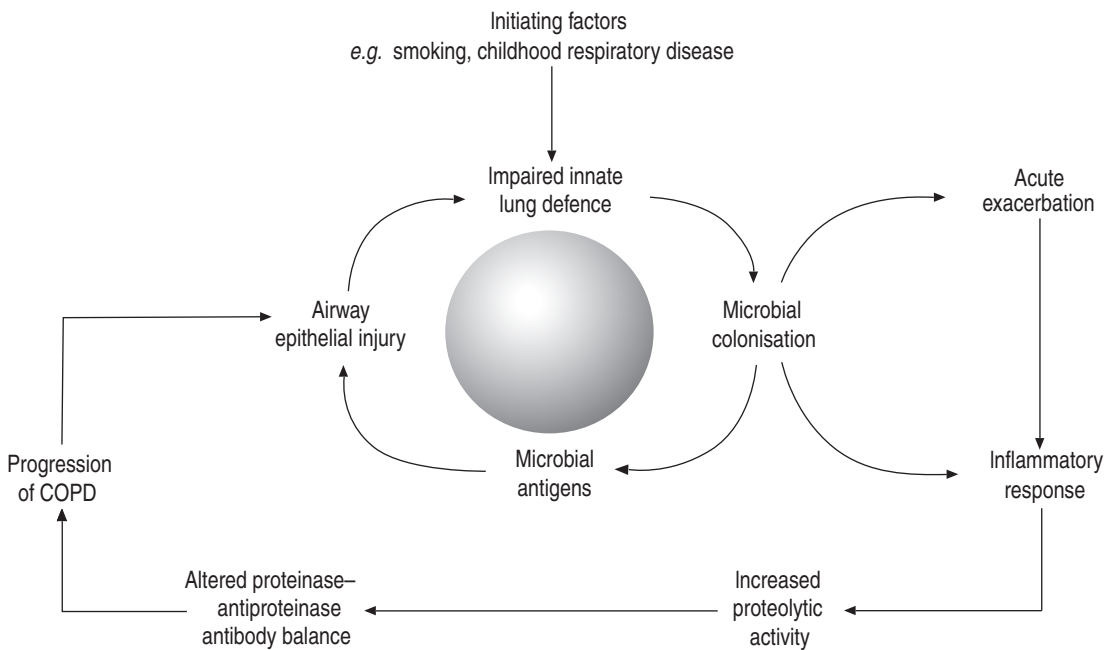


Figure 5. The vicious-circle hypothesis of infection and inflammation in COPD. After the initial insult impairs innate lung defence, bacterial colonisation perpetuates a cyclical sequence of events that contributes to the persistent inflammation and infection that are characteristic of COPD. Reproduced from [71] with permission from the publisher.

Surprisingly, the overall frequency of bronchiectasis in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Surrogate Endpoints) study was only 4% [113]. One reason for this difference may be due to the milder disease severity of the ECLIPSE cohort with a mean FEV₁ 48.3 % pred and nearly half of the cohort in GOLD stage II (Global Initiative for Chronic Obstructive Lung Disease), compared with 38.1 % pred in the study by PATEL *et al.* [112], although the incidence of bronchiectasis did increase with worsening disease severity.

The study by PATEL *et al.* [112] suggested that COPD may be a risk factor for bronchiectasis and such patients may represent a distinct phenotype. However, few studies investigating the relationship between COPD and bronchiectasis have since been carried out. More recently, factors associated with bronchiectasis in COPD patients attending specialist outpatient clinics were assessed [114]. In this study, 57.6% of stable COPD patients were found to have bronchiectasis on an HRCT image. Using a logistical model, the severity of airflow obstruction was the best predictor of underlying bronchiectasis. Other factors associated with bronchiectasis were the isolation of a PPM in sputum and at least one hospitalisation for an exacerbation of COPD, a marker of severe exacerbations, in the previous year (fig. 7) [114].

One of the major challenges in the comparison of clinical studies describing bronchiectasis in COPD patients is the wide range of CT findings that may be attributed to bronchiectasis, ranging from parabrachial infiltration and bronchial wall thickening to mucus plugging, dilated bronchi and emphysema. Clinical studies may also use different radiological scoring systems to determine the extent and severity of the underlying bronchiectasis [115, 116]. Therefore, a standardised

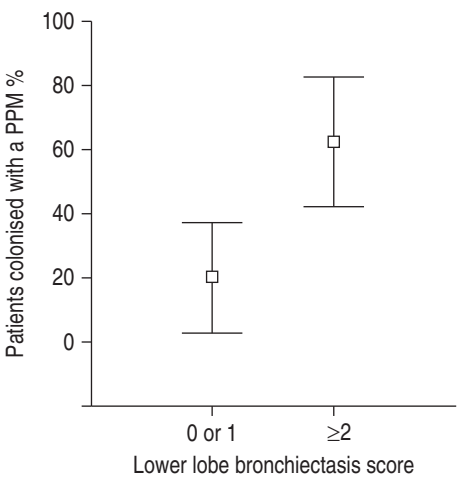


Figure 6. Relationship between the extent of lower lobe bronchiectasis and colonisation by potentially pathogenic microorganisms (PPM). Error bars are 95% confidence interval. $p=0.004$, odds ratio=7.0. Reproduced from [112] with permission from the publisher.

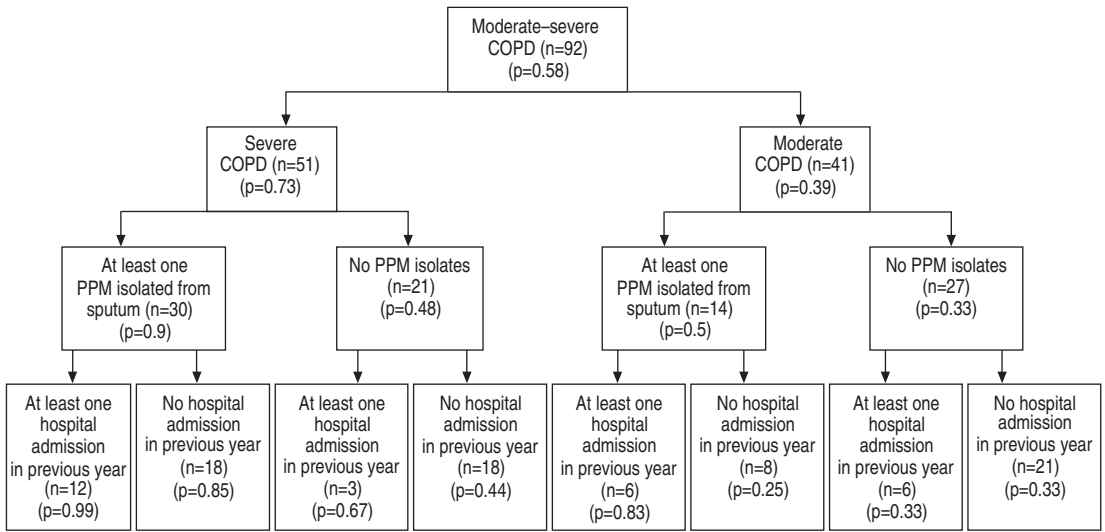


Figure 7. Probability of the presence of bronchiectasis in patients with moderate to severe COPD, by patient characteristics. PPM: potentially pathologic microorganism. Reproduced from [114] with permission from the publisher.

radiological definition and scoring system for bronchiectasis is much needed to enable comparison between clinical studies.

The clinical significance of these studies raises awareness of the overlap between bronchiectasis and COPD and highlights the relationship between structural and functional changes, which should be considered when assessing patients with COPD [117], particularly for the use of early antibiotics in the treatment of exacerbations. However, a conclusive causal relationship between COPD and bronchiectasis has yet to be determined and further longitudinal studies in larger populations will enable more accurate assessment of the incidence and prevalence of bronchiectasis. It was previously believed that established treatments for cystic-fibrosis (CF) related bronchiectasis could not be extrapolated to non-CF bronchiectasis and may actually do harm [118]. However, recent studies have demonstrated the beneficial effect of inhaled antibiotics [119, 120] and long-term macrolide therapy [121] in non-CF bronchiectasis, including patients with both bronchiectasis and COPD. As further additional trials in non-CF bronchiectasis using different inhaled antibiotics are underway, it is likely that future therapies for non-CF bronchiectasis will be similar to those already established in the management of CF.

Pulmonary aspergillosis

Aspergillus spp. comprise of ubiquitous fungi prevalent in both the outdoor and indoor environment. There are numerous species, although 90% of the fungal pathogens causing pulmonary disease are due to the inhalation of *Aspergillus fumigatus* or its spores [122]. *Aspergillus* spp. are airborne pathogens with a spore size of 2–3 µm, allowing them to reach the lung parenchyma *via* the airways. In a host with normal immunological defence mechanisms, specifically the innate immune response, exposure to *Aspergillus* spp. does not result in any adverse clinical sequelae [123]. However, in patients with COPD, reduced ciliary motility and impairment of antifungal effector cells, such as alveolar macrophages and neutrophils to phagocytise spores, contributes to an inability of the host to effectively remove spores from the airways and increasing the risk of invasive pulmonary aspergillosis (IPA) and more rarely chronic necrotising aspergillosis (CAN) [124, 125].

The most important risk factors for pulmonary aspergillosis are neutropenia, including haematopoietic stem-cell, and solid-organ transplants [126, 127]. However, increasing reports of fungal disease in patients without these classic risk factors, such as chronic lung disease and particularly COPD, have been published [128–133]. The incidence in COPD patients ranges from 1.3% [134] to 9% [135] and has been shown to be increasing more in recent years [133].

Similarly to pneumonia in COPD patients, risk factors in this group of patients also includes underlying disease severity [133], comorbidity and both prolonged and high-dose use of corticosteroids [128, 129, 132]. In addition, frequent exacerbations are often treated with broad-spectrum antibiotics, which have shown to be an independent predictor of IPA [133, 136], probably due to disruption of the usual microbial flora and predisposing to fungal growth.

The clinical presentation of IPA is often nonspecific or mimics exacerbations and combined with a low index of suspicion by treating physicians, the diagnosis of IPA may be delayed contributing to a high mortality rate observed in COPD patients [131, 132]. However, data are still limited to retrospective studies and further multicentre prospective work is required to further assess the risk and outcomes of IPA in COPD patients.

Conclusion

COPD is a complex, multidimensional disease with both pulmonary and extrapulmonary comorbidities playing a significant role in the natural history of the disease. Airway infection is an important aspect of the disease pathogenesis, worsening airway inflammation and subsequently increasing systemic inflammation, the latter being related to the increased risk of cardiovascular

disease seen in patients with COPD. Airway infection is not only seen in COPD exacerbations, but bacterial colonisation during periods of disease stability may increase the risk of pneumonia, leading to episodes of higher loads of potentially pathogenic microorganisms, which subsequently results in structural changes in the lung. This in turn, increases the risk of both typical and atypical infection, with a vicious cycle of airway and systemic inflammation of which exacerbations are a major cause. Thus, novel new treatments are urgently required both for the prevention and acute treatment of COPD exacerbations to improve the far-reaching consequences of this important disease.

Statement of Interest

J.A. Wedzicha has received honoraria for lectures and/or advisory boards from GSK, Astra Zeneca, Medimmune, Nycomed, Takeda, Pfizer, Chiesi, Boehringer Ingelheim, Novartis, Bayer, Vectura and Almirall. She has also received research grant funding for the institution from Novartis, Takeda, Chiesi and GSK.

References

1. Vestbo J, Hurd SS, Agusti AG, *et al.* Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, GOLD Executive Summary. *Am J Respir Crit Care Med* 2012; [Epub ahead of print DOI: 10.1164/rccm.201204-0596PP].
2. Patel AR, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. *Expert Rev Respir Med* 2011; 5: 647–662.
3. Kanner RE, Anthonisen NR, Connett JE, *et al.* Lower respiratory illnesses promote FEV₁ decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. *Am J Respir Crit Care Med* 2001; 164: 358–364.
4. Donaldson GC, Seemungal TA, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
5. Seemungal TA, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
6. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931.
7. Wedzicha JA, Seemungal TA, MacCallum PK, *et al.* Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000; 84: 210–215.
8. Hurst JR, Perera WR, Wilkinson TM, *et al.* Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 71–78.
9. Patel AR, Donaldson GC, Mackay AJ, *et al.* The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest* 2012; 141: 851–857.
10. Jousilahti P, Vartiainen E, Tuomilehto J, *et al.* Symptoms of chronic bronchitis and the risk of coronary disease. *Lancet* 1996; 348: 567–572.
11. Man SF, Connett JE, Anthonisen NR, *et al.* C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax* 2006; 61: 849–853.
12. Feary JR, Rodrigues LC, Smith CJ, *et al.* Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010; 65: 956–962.
13. Sin DD, Anthonisen NR, Soriano JB, *et al.* Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; 28: 1245–1257.
14. McGarvey LP, John M, Anderson JA, *et al.* Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; 62: 411–415.
15. Dahl M, Vestbo J, Lange P, *et al.* C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 250–255.
16. Danesh J, Collins R, Appleby P, *et al.* Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998; 279: 1477–1482.
17. Fisman EZ, Benderly M, Esper RJ, *et al.* Interleukin-6 and the risk of future cardiovascular events in patients with angina pectoris and/or healed myocardial infarction. *Am J Cardiol* 2006; 98: 14–18.
18. Jousilahti P, Salomaa V, Rasi V, *et al.* Symptoms of chronic bronchitis, haemostatic factors, and coronary heart disease risk. *Atherosclerosis* 1999; 142: 403–407.
19. Mannino DM, Valvi D, Mullerova H, *et al.* Fibrinogen, COPD and mortality in a nationally representative U.S. Cohort. *COPD* 2012; 9: 359–366.
20. Mackay AJ, Donaldson GC, Patel AR, *et al.* Usefulness of the Chronic Obstructive Pulmonary Disease Assessment Test to evaluate severity of COPD exacerbations. *Am J Respir Crit Care Med* 2012; 185: 1218–1224.

21. Koutsokera A, Kiropoulos TS, Nikoulis DJ, *et al.* Clinical, functional and biochemical changes during recovery from COPD exacerbations. *Respir Med* 2009; 103: 919–926.
22. Valipour A, Schreder M, Wolzt M, *et al.* Circulating vascular endothelial growth factor and systemic inflammatory markers in patients with stable and exacerbated chronic obstructive pulmonary disease. *Clin Sci (Lond)* 2008; 115: 225–232.
23. Kunter E, Ilvan A, Ozmen N, *et al.* Effect of corticosteroids on hemostasis and pulmonary arterial pressure during chronic obstructive pulmonary disease exacerbation. *Respiration* 2008; 75: 145–154.
24. Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
25. Banerjee D, Khair OA, Honeybourne D. Impact of sputum bacteria on airway inflammation and health status in clinical stable COPD. *Eur Respir J* 2004; 23: 685–691.
26. Donaldson GC, Seemungal TA, Patel IS, *et al.* Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest* 2005; 128: 1995–2004.
27. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007; 357: 2482–2494.
28. Maclay JD, McAllister DA, Johnston S, *et al.* Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax* 2011; 66: 769–774.
29. Oleksowicz L, Mrowiec Z, Zuckerman D, *et al.* Platelet activation induced by interleukin-6: evidence for a mechanism involving arachidonic acid metabolism. *Thromb Haemost* 1994; 72: 302–308.
30. Alber DG, Powell KL, Vallance P, *et al.* Herpesvirus infection accelerates atherosclerosis in the apolipoprotein E-deficient mouse. *Circulation* 2000; 102: 779–785.
31. Smeeth L, Thomas SL, Hall AJ, *et al.* Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004; 351: 2611–2618.
32. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. *Eur Heart J* 2008; 29: 96–103.
33. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis* 2009; 9: 601–610.
34. Gwini SM, Coupland CA, Siriwardena AN. The effect of influenza vaccination on risk of acute myocardial infarction: self-controlled case-series study. *Vaccine* 2011; 29: 1145–1149.
35. Donaldson GC, Hurst JR, Smith CJ, *et al.* Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.
36. von Hertzen LC. *Chlamydia pneumoniae* and its role in chronic obstructive pulmonary disease. *Ann Med* 1998; 30: 27–37.
37. Blasi F, Damato S, Cosentini R, *et al.* *Chlamydia pneumoniae* and chronic bronchitis: association with severity and bacterial clearance following treatment. *Thorax* 2002; 57: 672–676.
38. Saikku P, Leinonen M, Mattila K, *et al.* Serological evidence of an association of a novel *Chlamydia*, TWAR, with chronic coronary heart disease and acute myocardial infarction. *Lancet* 1988; 2: 983–986.
39. Gurfinkel E, Bozovich G, Beck E, *et al.* Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes: the final report of the ROXIS study. *Eur Heart J* 1999; 20: 121–127.
40. Gupta S, Leatham EW, Carrington D, *et al.* Elevated *Chlamydia pneumoniae* antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. *Circulation* 1997; 96: 404–407.
41. Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689–698.
42. Seemungal TA, Wilkinson TM, Hurst JR, *et al.* Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008; 178: 1139–1147.
43. Diederens BM, van der Valk PD, Kluytmans JA, *et al.* The role of atypical respiratory pathogens in exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007; 30: 240–244.
44. Garcha DS, Thurston SJ, Patel AR, *et al.* Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012; 67: 1078–1080.
45. Seemungal TA, Wedzicha JA, MacCallum PK, *et al.* *Chlamydia pneumoniae* and COPD exacerbation. *Thorax* 2002; 57: 1087–1088.
46. Baker EH, Janaway CH, Philips BJ, *et al.* Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 2006; 61: 284–289.
47. Chakrabarti B, Angus RM, Agarwal S, *et al.* Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD. *Thorax* 2009; 64: 857–862.
48. Bolton CE, Evans M, Ionescu AA, *et al.* Insulin resistance and inflammation – a further systemic complication of COPD. *COPD* 2007; 4: 121–126.
49. Heron M. Deaths: leading causes for 2008. *Natl Vital Stat Rep* 2012; 60: 1–94.
50. World Health Organization. The Top 10 Causes of Death. Fact Sheet. Geneva, World Health Organization, 2011. who.int/mediacentre/factsheets/fs310/en/index.html. Date last updated June 2011. Date last accessed: August 5, 2012.
51. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012; 67: 71–79.

52. Ruiz M, Ewig S, Marcos MA, *et al.* Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am J Respir Crit Care Med* 1999; 160: 397–405.
53. Falguera M, Martín M, Ruiz-González A, *et al.* Community-acquired pneumonia as the initial manifestation of serious underlying diseases. *Am J Med* 2005; 118: 378–383.
54. Niederman MS, McCombs JS, Unger AN, *et al.* The cost of treating community-acquired pneumonia. *Clin Ther* 1998; 20: 820–837.
55. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii55.
56. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J* 2003; Suppl. 41, 46s–53s.
57. Anthonisen NR, Manfreda J, Warren CP, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
58. Hurst JR, Wedzicha JA. Management and prevention of chronic obstructive pulmonary disease exacerbations: a state of the art review. *BMC Med* 2009; 7: 40.
59. Restrepo MI, Mortensen EM, Pugh JA, *et al.* COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur Respir J* 2006; 28: 346–351.
60. Pifarre R, Falguera M, Vicente-de-Vera C, *et al.* Characteristics of community-acquired pneumonia in patients with chronic obstructive pulmonary disease. *Respir Med* 2007; 101: 2139–2144.
61. Molinos L, Clemente MG, Miranda B, *et al.* Community-acquired pneumonia in patients with and without chronic obstructive pulmonary disease. *J Infect* 2009; 58: 417–424.
62. Müllerova H, Chigbo C, Hagan GW, *et al.* The natural history of community-acquired pneumonia in COPD patients: a population database analysis. *Respir Med* 2012; 106: 1124–1133.
63. Myles PR, McKeever TM, Pogson Z, *et al.* The incidence of pneumonia using data from a computerized general practice database. *Epidemiol Infect* 2009; 137: 709–716.
64. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case-control study. *Br J Gen Pract* 2009; 59: e329–e338.
65. van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet* 2009; 374: 1543–1556.
66. Cillóniz C, Ewig S, Polverino E, *et al.* Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011; 66: 340–346.
67. Soler N, Ewig S, Torres A, *et al.* Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. *Eur Respir J* 1999; 14: 1015–1022.
68. Zalacain R, Sobradillo V, Amilibia J, *et al.* Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 1999; 13: 343–348.
69. Monsó E, Rosell A, Bonet G, *et al.* Risk factors for lower airway bacterial colonization in chronic bronchitis. *Eur Respir J* 1999; 13: 338–342.
70. Patel IS, Seemungal TA, Wilks M, *et al.* Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax* 2002; 57: 759–764.
71. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355–2365.
72. Ostergaard L, Andersen PL. Etiology of community-acquired pneumonia: evaluation by transtracheal aspiration, blood culture, or serology. *Chest* 1993; 104: 1400–1407.
73. Torres A, Dorca J, Zalacain R, *et al.* Community-acquired pneumonia in chronic obstructive pulmonary disease: a Spanish multicenter study. *Am J Respir Crit Care Med* 1996; 154: 1456–1461.
74. Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163: 1730–1754.
75. García-Vidal C, Almagro P, Román V, *et al.* *Pseudomonas aeruginosa* in patients hospitalised for COPD exacerbation: a prospective study. *Eur Respir J* 2009; 34: 1072–1078.
76. Miravittles M, Espinosa C, Fernandez-Laso E, *et al.* Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD: study group of bacterial infection in COPD. *Chest* 1999; 116: 40–46.
77. Marrie TJ. Bacteraemic pneumococcal pneumonia: a continuously evolving disease. *J Infect* 1992; 24: 247–255.
78. Calbo E, Valdes E, Ochoa de Echaguen A, *et al.* Bacteraemic pneumococcal pneumonia in COPD patients: better outcomes than expected. *Eur J Clin Microbiol Infect Dis* 2009; 28: 971–976.
79. Cillóniz C, Ewig S, Polverino E, *et al.* Pulmonary complications of pneumococcal community-acquired pneumonia: incidence, predictors, and outcomes. *Clin Microbiol Infect*, 18: 1134–1142.
80. Gutierrez P, Closa D, Piner R, *et al.* Macrophage activation in exacerbated COPD with and without community-acquired pneumonia. *Eur Respir J* 2010; 36: 285–291.
81. Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
82. Crim C, Calverley PM, Anderson JA, *et al.* Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009; 34: 641–647.

83. Calverley PM, Stockley RA, Seemungal TA, *et al.* Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest* 2011; 139: 505–512.
84. Drummond MB, Dasenbrook EC, Pitz MW, *et al.* Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008; 300: 2407–2416.
85. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med* 2009; 169: 219–229.
86. Ernst P, Gonzalez AV, Brassard P, *et al.* Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med* 2007; 176: 162–166.
87. Chen D, Restrepo MI, Fine MJ, *et al.* Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia. *Am J Respir Crit Care Med* 2011; 184: 312–316.
88. Malo de Molina R, Mortensen EM, Restrepo MI, *et al.* Inhaled corticosteroid use is associated with lower mortality for subjects with COPD and hospitalised with pneumonia. *Eur Respir J* 2010; 36: 751–757.
89. Mortimer KJ, Tattersfield AE, Tang Y, *et al.* Plasma concentrations of fluticasone propionate and budesonide following inhalation: effect of induced bronchoconstriction. *Br J Clin Pharmacol* 2007; 64: 439–444.
90. Sin DD, Tashkin D, Zhang X, *et al.* Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet* 2009; 374: 712–719.
91. Edwards MR, Bartlett NW, Clarke D, *et al.* Targeting the NF- κ B pathway in asthma and chronic obstructive pulmonary disease. *Pharmacol* 2009; 121: 1–13.
92. Di Stefano A, Caramori G, Oates T, *et al.* Increased expression of nuclear factor- κ B in bronchial biopsies from smokers and patients with COPD. *Eur Respir J* 2002; 20: 556–563.
93. Hill AT, Campbell EJ, Hill SL, *et al.* Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000; 109: 288–295.
94. Wilkinson TM, Patel IS, Wilks M, *et al.* Airway bacterial load and FEV₁ decline in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 167: 1090–1095.
95. Patterson CM, Morrison RL, D'Souza A, *et al.* Inhaled fluticasone propionate impairs pulmonary clearance of *Klebsiella Pneumoniae* in mice. *Respir Res* 2012; 13: 40.
96. Falkinham JO 3rd. Nontuberculous mycobacteria in the environment. *Clin Chest Med* 2002; 23: 529–551.
97. von Reyn CF, Arbeit RD, Horsburgh CR, *et al.* Sources of disseminated *Mycobacterium avium* infection in AIDS. *J Infect* 2002; 44: 166–170.
98. Sexton P, Harrison AC. Susceptibility to nontuberculous mycobacterial lung disease. *Eur Respir J* 2008; 31: 1322–1333.
99. Griffith DE, Aksamit T, Brown-Elliott BA, *et al.* An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367–416.
100. Dailloux M, Abalain ML, Laurain C, *et al.* Respiratory infections associated with nontuberculous mycobacteria in non-HIV patients. *Eur Respir J* 2006; 28: 1211–1215.
101. Andr  jak C, Thomsen V  , Johansen IS, *et al.* Nontuberculous pulmonary mycobacteriosis in Denmark: incidence and prognostic factors. *Am J Respir Crit Care Med* 2010; 181: 514–521.
102. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. *Annu Rev Immunol* 2002; 20: 581–620.
103. Horsburgh CR Jr, Selik RM. The epidemiology of disseminated nontuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). *Am Rev Respir Dis* 1989; 139: 4–7.
104. Ergin A, Hascelik G. Non tuberculous mycobacteria (NTM) in patients with underlying diseases: results obtained by using polymerase chain reaction-restriction enzyme analysis between 1997–2002. *New Microbiol* 2004; 27: 49–53.
105. Teo SK, Lo KL. Nontuberculous mycobacterial disease of the lungs in Singapore. *Singapore Med J* 1992; 33: 464–466.
106. Winthrop KL, McNelley E, Kendall B, *et al.* Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. *Am J Respir Crit Care Med* 2010; 182: 977–982.
107. Andrejak C, Nielsen R, Thomsen VO, *et al.* Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* 2012 [Epub ahead of print DOI: 10.1136/thoraxjnl-2012-201772].
108. Donnelly LE, Barnes PJ. Defective phagocytosis in airways disease. *Chest* 2012; 141: 1055–1062.
109. Sethi S, Maloney J, Grove L, *et al.* Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 991–998.
110. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; 65, Suppl 1, i1–i58.
111. O'Brien C, Guest PJ, Hill SL, *et al.* Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635–642.
112. Patel IS, Vlahos I, Wilkinson TM, *et al.* Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400–407.
113. Agusti A, Calverley PM, Celli B, *et al.* Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; 11: 122.
114. Mart  nez-Garc  a M  , Soler-Catalu  a JJ, Donat Sanz Y, *et al.* Factors associated with bronchiectasis in patients with COPD. *Chest* 2011; 140: 1130–1137.
115. Bhalla M, Turcios N, Aponte V, *et al.* Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; 179: 783–788.

116. Smith IE, Jurriaans E, Diederich S, *et al.* Chronic sputum production: correlations between clinical features and findings on high resolution computed tomographic scanning of the chest. *Thorax* 1996; 51: 914–918.
117. Wedzicha JA, Hurst JR. Structural and functional co-conspirators in chronic obstructive pulmonary disease exacerbations. *Proc Am Thorac Soc* 2007; 4: 602–605.
118. O'Donnell AE. Bronchiectasis. *Chest* 2008; 134: 815–823.
119. Murray MP, Govan JR, Doherty CJ, *et al.* A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2011; 183: 491–499.
120. Wilson R, Welte T, Polverino E, *et al.* Ciprofloxacin DPI in non-cystic fibrosis bronchiectasis: a phase II randomised study. *Eur Respir J* 2012 [Epub ahead of print DOI: 10.1183/09031936.00071312].
121. Wong C, Jayaram L, Karalus N, *et al.* Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 660–667.
122. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2007; 30: 782–800.
123. Latgé JP. The pathobiology of *Aspergillus fumigatus*. *Trends Microbiol* 2001; 9: 382–389.
124. Shoham S, Levitz SM. The immune response to fungal infections. *Br J Haematol.* 2005; 129: 569–582.
125. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. *Eur Respir Rev* 2011; 20: 156–174.
126. Gerson SL, Talbot GH, Hurwitz S, *et al.* Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. *Ann Intern Med* 1984; 100: 345–351.
127. Segal BH, Walsh TJ. Current approaches to diagnosis and treatment of invasive aspergillosis. *Am J Respir Crit Care Med* 2006; 173: 707–717.
128. Barouky R, Badet M, Denis MS, *et al.* Inhaled corticosteroids in chronic obstructive pulmonary disease and disseminated aspergillosis. *Eur J Intern Med* 2003; 14: 380–382.
129. Cornet M, Mallat H, Somme D, *et al.* Fulminant invasive pulmonary aspergillosis in immunocompetent patients—a two-case report. *Clin Microbiol Infect* 2003; 9: 1224–1227.
130. Ader F, Nseir S, Le Berre R, *et al.* Invasive pulmonary aspergillosis in chronic obstructive pulmonary disease: an emerging fungal pathogen. *Clin Microbiol Infect* 2005; 11: 427–429.
131. Carrascosa Porras M, Herreras Martínez R, Corral Mones J, *et al.* Fatal *Aspergillus* myocarditis following short-term corticosteroid therapy for chronic obstructive pulmonary disease. *Scand J Infect Dis* 2002; 34: 224–227.
132. Samarakoon P, Soubani AO. Invasive pulmonary aspergillosis in patients with COPD: a report of five cases and systematic review of the literature. *Chron Respir Dis* 2008; 5: 19–27.
133. Guinea J, Torres-Narbona M, Gijon P, *et al.* Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. *Clin Microbiol Infect* 2010; 16: 870–877.
134. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001; 32: 358–366.
135. Patterson TF, Kirkpatrick WR, White M, *et al.* Invasive aspergillosis disease spectrum, treatment practices, and outcomes. *Medicine (Baltimore)* 2000; 79: 250–260.
136. Khasawneh F, Mohamad T, Moughrabieh MK, *et al.* Isolation of *Aspergillus* in critically ill patients: a potential marker of poor outcome. *J Crit Care* 2006; 21: 322–327.

Chapter 6

Malnutrition and obesity in COPD



Erica P.A. Rutten*, Emiel F.M. Wouters[#] and Frits M.E. Franssen*

SUMMARY: With regard to the systemic complexity of COPD, differences in body composition are among the most extensively investigated. As such, malnutrition has been widely studied in relation to COPD, and contributes to a decreased performance in addition to worse prognosis. Patients with COPD have higher prevalence of malnutrition compared to non-COPD subjects, and several risk factors have been identified. However, future research should focus on the pathophysiology of the development of malnutrition in COPD, as recent findings show that the progressive decline of lean mass is not disease specific *per se*. Furthermore, obesity in COPD is increasing as there might be a complex inter-relationship between the adipose tissue and impaired oxygen availability. However, the impact of obesity on exercise capacity in COPD is dependent on the type of exercise, with obesity being associated with decreased tolerance to weight-bearing exercise while having beneficial effects on dynamic ventilatory mechanics during weight-supported exercise. In contrast to early stage COPD, obesity seems to protect against mortality in patients with severe disease. Treatment of malnutrition and obesity in COPD should be multidisciplinary, as is included in a pulmonary rehabilitation programme.

KEYWORDS: Adipose tissue, exercise tolerance, malnutrition, metabolic syndrome, obesity, skeletal muscle mass

*Program Development Centre, Centre of Expertise for Chronic Organ Failure (CIRO⁺), Horn, and [#]Dept of Respiratory Medicine, Maastricht University Medical Centre, Maastricht University, Maastricht, The Netherlands.

Correspondence: E.P.A. Rutten, Program Development Centre, CIRO⁺, Hornerheide 1, 6085 NM Horn, The Netherlands. Email: ericarutten@ciro-horn.nl

Eur Respir Monogr 2013; 59: 80–92.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10039912
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

As early as the 1960s, FILLEY *et al.* [1] distinguished two phenotypes in COPD: the pink puffers being “thin in appearance with frequent history of major weight loss” and the blue bloaters identified as “no marked weight loss except terminally”. Today, the two phenotypes, malnutrition and obesity, are still being researched in COPD as the inter-relationship between both phenotypes and COPD is complex, and both malnutrition and obesity contribute to the patient’s morbidity and mortality risk. Although the underlying mechanisms are not fully clear, it is becoming more and more obvious that the treatment of both malnutrition and obesity should be multidisciplinary. The purpose of the present chapter is to summarise the available knowledge about the two phenotypes in relation to COPD (fig. 1).

Malnutrition

“Malnutrition” is defined as the condition that develops when the body does not get the right amount of the vitamins, minerals and other nutrients it needs to maintain healthy tissues and organ function [2]. In relation to COPD, a whole batch of terms including malnutrition, muscle wasting, depletion and cachexia have been introduced that refer to a thin body shape as a result of low body mass and/or low skeletal muscle mass. However, it took until the 1990s for the condition of malnutrition to receive more attention and for the relevance of body composition assessment in COPD patients to be demonstrated [3]. Currently, a new debate exists concerning the definition and the progression of a thin body shape in COPD. Herein, the available literature is summarised.

Low body mass index

A decrease in body weight is primarily a consequence of an imbalance of nutritional intake and energy expenditure. In COPD, lack of appetite is suggested as a consequence of dyspnoea [4], and meal ingestion could induce a drop in arterial oxygen saturation [5]. However, an inadequate nutritional intake could not be proven in a Spanish group of COPD patients [6], although dietary intake is not well established in malnourished patients with COPD. However, alterations in energy expenditure are more extensively investigated. Total energy expenditure represents the sum of resting energy expenditure (~60%), diet-induced energy expenditure (~10%) and physical activity-induced energy expenditure (~30%). Thus, resting energy expenditure represents the largest amount by far. It has been shown that in male patients with COPD the absolute value of the adjusted resting energy expenditure, as well as the percentage of subjects with hypermetabolism, was higher in a random group of COPD patients compared to the control subjects [7, 8]. Although an alteration in activity-induced energy expenditure has not yet been shown in COPD, research has shown lower leg mechanical efficiency in COPD patients [7]. This could be a compensatory mechanism for higher activity-induced energy expenditure, but it could also be the cause of a general decrease in physical activity.

Low body mass index (BMI) was associated with a higher risk of dying in clinically stable patients with COPD, as well as in hospitalised patients with exacerbations [9–11]. Subsequently, as the BMI is an easy to use and cheap measure of nutritional status, a multi-dimensional index, the BODE (BMI, airflow obstruction, dyspnoea, exercise capacity) index, was created and was a better predictor of risk of death from any cause or from respiratory causes than the severity of airflow limitation alone [12]. However, a shortcoming of the BMI is that normal body weight can cover low muscle mass in the presence of elevated levels of fat mass [13, 14]. Since a low skeletal muscle mass has been shown to be independently involved in the prognosis of COPD, attention is now directed from the whole body mass to the two-compartment assessment of body composition, fat mass and skeletal muscle mass.

Low fat-free mass

Skeletal muscle mass represents ~10-20% of the total body weight and is assumed to be the most active metabolic component of the body. Noninvasive assessment of the skeletal muscle mass can be derived from the assessment of the fat-free mass by, for example, dual X-ray absorptiometry or bio-electrical impedance. Therefore, fat-free mass divided by the square of height, the fat-free mass index, is used as a surrogate marker for skeletal muscle mass. In COPD, fat-free mass has been detected as an independent



Figure 1. Malnutrition and obesity in COPD.

determinant for exercise tolerance [7, 15, 16]. In addition, low muscle mass has been associated with impaired disease-specific health status [17, 18] and with increased mortality risk [19, 20].

The prevalence of a low skeletal muscle mass has been documented widely and ranges from almost 20% in mild-to-moderate COPD patients [21–23] to ~40% in severe patients with COPD [22, 23] and to >50% in complex patients with acute lung failure [24]. Only recently, some reports compared the prevalence of a low muscle mass in patients with COPD with that of non-COPD subjects matched for age. A large Norwegian cohort reported that ~30% of the patients with clinically diagnosed COPD and about 10% of the current or former smoking subjects without COPD had a low fat-free mass index [25]. Indeed, a lower lean mass in subjects with obstructive lung disease compared to former and never-smoking controls was confirmed in the American Health ABC study, but this was not true when compared to current smoking controls [26].

Physiology of loss of muscle mass in COPD

It is believed that the development of a low muscle mass is a form of myopathy involving a whole cascade of modifications directly or indirectly related to the underlying disease. To start, histological changes in the skeletal muscle of patients with COPD have been shown. As such, reduced muscle-to-capillary interface was present in normal weight patients with COPD, which was associated with decreased exercise capacity [27]. Furthermore, reduced oxidative fibres in favour of the glycolytic fibres have been shown in patients with COPD [28], and these were related to the reduced oxidative capacity [29]. This fibre type shifting was correlated with BMI, as was concluded from a meta-analysis [30]. Furthermore, the cross-sectional area measured by ultrasonography was reduced in a random sample of COPD patients and contributed to the physical inactivity [31]. To date, muscle mass can only decrease when there is an imbalance between the muscle protein breakdown and protein synthesis. Both increased whole body protein synthesis and breakdown have been shown in normal weight patients with COPD [32]. Various studies using different techniques revealed an increased whole body and myofibrillar protein breakdown in patients with decreased body weight and muscle mass compared to normal weight patients and healthy controls [33–35]. However, these studies did not measure protein synthesis. The constituents of protein are amino acids, and several reports showed disturbances in plasma and skeletal muscle concentrations of anaplerotic amino acids, the branched-chain amino acids (leucine, isoleucine and valine) and glutamate concentration in malnourished patients with COPD [33, 36–39]. Together with the finding that increased glucose turnover is predominantly present in underweight patients with COPD [40], there is an indication that alterations in substrate metabolism are present in malnourished COPD patients. On a molecular level, skeletal muscle protein metabolism is regulated by the ubiquitin–proteasome pathway that regulates the protein breakdown, while the MyoD regulated myogenesis is involved in muscle protein synthesis [41]. There is indirect evidence from *in vitro* studies that both pathways are involved in the disturbed protein metabolism in patients with COPD [42, 43], but clinical confirmation is lacking at present.

Factors contributing to a low muscle mass in COPD

Multiple factors could contribute to a lower lean mass in COPD. To start with, COPD is a disease mainly affecting the elderly population. In parallel, a decrease in skeletal muscle mass also mainly happens later in life. It has recently been shown that COPD is a syndrome of accelerated lung ageing [44, 45]. Whether the effects of accelerated ageing contribute to a higher prevalence of malnutrition in COPD remains to be investigated. Furthermore, as patients with COPD are physically less active compared to their control peers [46], muscle disuse by itself leads to adaptive changes in skeletal muscle. However, loss of skeletal muscle mass in patients with chronic disease is not equal to inactivity-induced loss of fat-free mass alone [7]. As the occurrence of exacerbations was associated with a higher decline in fat-free mass index, it could be another factor that may contribute to a low muscle mass [47]. Indeed, oral glucocorticoids have been proposed as a significant cause of skeletal muscle impairment [48]. In addition, hypoxia is frequently present in patients with COPD and could contribute to malnutrition *via* various pathways [49]. In line with this, external oxygen supplementation patients with severe COPD resulted in improvement of the

exercise tolerance [50]. However, no direct link between hypoxia and malnutrition in COPD has been found. Patients with COPD often suffer from low-grade systemic inflammation, even in a clinically stable condition. Research on the effects of pro-inflammatory cytokines on skeletal muscle metabolism revealed an effect on the ubiquitin–proteasome pathway [51, 52], as well as on muscle regeneration [53], but supporting clinical data are lacking. Although indirect evidence suggests a link between systemic inflammation and muscle atrophy [54], a recently published article stated that it could not be confirmed as to whether systemic inflammation is a cause of an accelerated loss of fat-free mass in COPD [55].

Effect of low muscle mass in combination with high fat mass

Since it has become clear that the adipose tissue is not a single storage pool but an active endocrine organ, research is focussing on the effect of high adipose tissue in combination with low muscle mass in patients with COPD. Elevated plasma C-reactive protein (CRP) levels have been reported in patients with abdominal obesity irrespective of the amount of muscle mass [56]. In addition, plasma levels of inflammatory markers were positively associated with fat mass and not with fat-free mass in approximately 400 clinically stable COPD patients from the Bergen COPD Cohort Study [57]. No studies are currently available about the inter-relationship between the pro-inflammatory actions of the adipose tissue on the skeletal muscle mass in COPD, but this should be performed in the near future.

Old thoughts versus new perspectives

As can be concluded from previous studies, evidence exists that low skeletal muscle mass is more prevalent in patients with COPD compared to elderly patients without coexisting COPD. Furthermore, malnutrition is detrimental for patients functioning, well-being and prognosis. The previously mentioned studies, however, cannot give any conclusion about the progressive decline of muscle mass in comparison with an elderly population without COPD as most of these studies are limited due to their cross-sectional study design. In this respect, it could be that patients with COPD start with a lower lean mass but that the progressive decline is comparable with the physiological sarcopenia syndrome that occurs in the “healthy” elderly. The results of the longitudinal analyses of the American Health ABC cohort support this hypothesis [26]. Indeed, the negative slope of the lean mass over 8 years was equal in the patients with obstructive lung disease and the smoking, former smoking and never-smoking control subjects. Whether the higher prevalence of malnutrition in COPD is due to the development early in the disease course, as a cause of smoking, or whether thin subjects are more prone to develop COPD is not known yet. The latter is, however, supported by recent data of the BOLD (Burden of Obstructive Lung Disease) study showing that lean never-smoking subjects had a higher risk of developing COPD [58]. Nevertheless, these data imply that the progressive decline of muscle mass is not disease specific *per se*. Only one previous study has evaluated fat-free mass over 1 year in a relatively small group of COPD patients [47]. The overall fat-free mass remained stable over 1 year, although in eight patients who were on long-term corticosteroids the decline in fat-free mass was higher compared to the rest of the group. Taken together, these data shed new light on the concept of COPD as a chronic wasting syndrome, and challenge us to reposition the systemic complexity of COPD. Noticeably, it is probable that a subgroup of COPD patients who are prone to suffer from accelerated weight or muscle loss exists. Although future research should characterise this phenotype, there is indirect evidence that is a group of patients with frequent exacerbations [47]. As patients with weight loss over 5 years have worse prognosis [59], nutritional management in COPD should focus on the prevention of weight loss.

How to treat malnutrition in COPD

Nutritional supplementation in malnourished patients with COPD is being extensively investigated [60, 61]. Taken together, it is possible to enhance energy and protein intake with oral nutritional supplementation in malnourished patients with COPD. Moreover, during the intervention, body weight increases in favour of the treated group, but it is not unambiguous that the increase is due to an increase in muscle mass rather than fat mass. It has recently been

confirmed that the combination of nutritional intake and physical exercise appears more beneficial in increasing muscle mass, muscle strength and disease-related quality of life [62–64], even in severe patients with COPD suffering from exacerbations [65]. Furthermore, although the gain in fat-free mass during a nutritional rehabilitation is relatively small, the gain in fat-free mass was significantly higher in the muscle wasted patients [66]. Nevertheless, intensive follow-up care is needed in order to maintain the gain in skeletal muscle mass and physical functioning [66]. In relation to the abovementioned new perspectives, future studies should focus on the effects of nutritional supplementation in patients who are losing weight, although it should be kept in mind that finding the cause of the weight loss is of primordial importance to prescribe an accurate treatment.

Obesity

While traditionally considered a wasting disease, characterised by involuntary weight loss and depletion of muscle mass, there is an increasing focus on the impact of obesity in patients with COPD. In this section, the epidemiology of obesity, defined as $\text{BMI} \geq 30 \text{ kg}\cdot\text{m}^{-2}$, and its impact on symptoms, lung function, exercise performance and survival in COPD will be described. In addition, the potential role of metabolic syndrome and adipose tissue dysfunction in COPD pathophysiology will be evaluated. Finally, management of obesity in COPD and the effects of pulmonary rehabilitation will be discussed.

Epidemiology

Whereas the worldwide prevalence of obesity has more than doubled in the last three decades [67], there are only limited data on trends in prevalence of obesity in patients with COPD. In the Canadian National Health Survey, the prevalence of obesity in subjects with self-reported COPD increased by 5% over a 14-year period, while it increased 38% in non-COPD subjects over the same period [68]. In the same study, the prevalence of obesity in COPD and non-COPD subjects was 24.6% and 17.1%, respectively. An even higher prevalence of obesity was reported in an adult multi-ethnic cohort of early stage COPD patients from Northern California, USA [69]. In this study, 54% of subjects met criteria for obesity compared to the 20–24% reported prevalence for the general adult population of that region. However, not all studies reported increased prevalence of obesity in COPD compared to non-COPD subjects. In the multicentre population-based epidemiological PLATINO (Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar) study, the prevalence of obesity among those meeting spirometric criteria for COPD (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 0.7) was 23%, compared to 32% in subjects without COPD [70]. In another study from the Netherlands, based on a large primary care population of COPD patients, the prevalence of obesity was 18% [23]. In that cohort, obesity was found to be more prevalent (16–24%) in patients with milder disease severity (Global Initiative for Chronic Obstructive Lung Disease (GOLD) I and II) and was lowest (6%) in those with severe disease (GOLD IV) [23]. This is compared to the national prevalence of obesity in the general adult population in the Netherlands, which, at that time, was approximately 11% [71].

As such, available data indicate that the prevalence of obesity in COPD is variable and may be related to differences in general risk factors for obesity among populations, such as sex, diet, level of daily physical activity and education [68]. In addition, factors related to COPD disease severity, including the severity of airflow limitation, frequency of exacerbations and hospitalisations, comorbidities, use of systemic glucocorticosteroids and smoking status, may also contribute to the observed differences in prevalence of obesity between studies.

Symptoms

It has long been recognised that obese individuals experience increased symptoms of dyspnoea and more exercise limitation than non-obese individuals, independent of the presence of airflow

limitation [72]. In a recent study including adult subjects without an established diagnosis of COPD, obesity and not airflow limitation was associated with productive cough, exercise-induced dyspnoea, poor self-reported health and decreased functional performance [73]. In addition, in a COPD population, obese patients reported increased dyspnoea and poorer health-related quality of life than normal-weight patients [74]. Remarkably, the number of inhaled medications was higher in obese patients compared to normal-weight patients despite having less severe chronic airflow limitation [74]. Also, the level of fatigue seems to be increased in obese compared to non-obese COPD patients [75].

Lung function

A reduction in functional residual capacity (FRC) as a result of a reduction in lung compliance [76] is the most prominent effect of obesity on respiratory function in both normal subjects [77] as well as patients with COPD [78]. In a study of moderate-to-severe COPD patients, there was no difference in diffusion capacity or maximum inspiratory mouth occlusion pressure between normal weight and obese patients with a comparable degree of airflow limitation [78]. Although resting hyperinflation was present in both groups, FRC and expiratory reserve volume were significantly lower in obese patients compared to normal-weight patients [78]. This was probably due to the effects of obesity on static lung volumes in COPD causing less hyperinflation. Similarly, total lung capacity (TLC) (% predicted) was smaller and the ratio of inspiratory capacity (IC) to TLC was significantly increased in obese compared to normal-weight COPD patients. In line with isolated obesity, increasing BMI was associated with decreasing static lung volumes in COPD [78], resulting in less hyperinflation. The association between BMI and plethysmographically measured lung volumes was shown to be independent of the severity of COPD [79]. However, increasing BMI was found to be associated with increasing FEV₁/FVC ratio, especially in patients with severe to very severe disease [79]. Whether the observed effects of obesity on lung function in COPD patients differ based on distribution of fat mass (*i.e.* central *versus* peripheral obesity) has not yet been studied.

Exercise performance

Despite the increased resting and exercise-induced metabolic needs, peak cycling exercise capacity has been shown to be normal in healthy obese subjects compared to normal-weight, age-matched controls [80]. Also, in obese patients with COPD, peak oxygen uptake and peak work rate during symptom-limited cycle exercise were higher compared to normal-weight patients matched for FEV₁ [78]. Although both patient groups had ventilatory exercise limitation, minute ventilation and ventilatory efficiency at any given work rate were greater in the obese patients. Dyspnoea intensity at any given level of ventilation was also lower in obese COPD patients compared to normal weight patients [78], despite a higher respiratory rate in the obese patients. This lowered dyspnoea intensity in the obese COPD subjects is probably the result of improved ventilatory mechanics. Although the magnitude of dynamic hyperinflation was comparable to the normal weight COPD patients, the relative dynamic end-expiratory lung volume was lower during exercise in the obese patients [78], resulting in a higher maximal minute ventilation.

In contrast to cycling, which is a non-weight bearing exercise, important impairments in weight-bearing exercises were reported in obese COPD patients. In COPD patients referred for pulmonary rehabilitation, 6-minute walking distance and functional status were significantly reduced in obese patients compared to non-obese patients with an even more impaired lung function [75]. This is probably due to increased metabolic and ventilatory requirements associated with weight-bearing exercise, given comparable physiological responses, *i.e.* dyspnoea and leg fatigue during the 6-minute walking test, between obese and non-obese COPD patients [81]. Thus, the potential beneficial influence of obesity on exercise tolerance related to decreased resting hyperinflation may be offset by the increased metabolic load associated with weight-bearing exercise in obesity. Future studies need to clarify the influence of obesity on activities of daily life in COPD.

Effect of obesity on prognosis in COPD

In the general population, obesity is associated with a large decrease in life expectancy [82]. In the Prospective Studies Collaboration the association between BMI and mortality was assessed by long-term prospective follow-up of almost 900,000 participants [83]. For each $5\text{-kg}\cdot\text{m}^{-2}$ increase in BMI above the normal range, overall mortality was about 30% higher, mainly due to cardiovascular disease [83].

Few studies have investigated the impact of obesity on prognosis in patients with COPD. In the epidemiological Copenhagen City Heart Study, obesity was associated with a 20–34% increase in the relative risk of all-cause mortality in patients with mild-to-moderate COPD compared to normal BMI patients with comparable disease severity [10]. However, the relative risk of all-cause mortality and COPD-related mortality was 0.62 and 0.31, respectively, in patients with severe COPD compared to normal weight patients with severe disease [10]. A possibly protective role for obesity in patients with severe COPD was also observed in early studies on the association between body weight and mortality [84, 85]. In the ANTADIR (Association Nationale pour le Traitement a Domicile de l'Insuffisance Respiratoire Chronique) network, the prognostic value of obesity in hypoxaemic patients with COPD treated with long-term oxygen therapy was clearly demonstrated [9]. During the 7.5 years of follow-up, the highest survival and lowest hospitalisation rates were observed in obese COPD patients. The 5-year survival rates for patients with a BMI <20 , 20–24, 25–29 and $>30\text{ kg}\cdot\text{m}^{-2}$ were 24%, 34%, 44% and 59%, respectively. Thus, this possible association between obesity and improved survival in COPD contrasts with epidemiological data from the general population. Although not completely understood, this phenomenon, known as the “obesity paradox”, is not unique to COPD [86]. One explanation for the prognostic advantage of obesity concerns the relative reduction in static lung volumes in obese COPD patients. During a 3-year follow-up study, the IC/TLC ratio, an index of static lung hyperinflation, was found to be an independent predictor of increased respiratory and all-cause mortality in patients with COPD [87]. Although the mechanism underlying the association between hyperinflation and prognosis remains unclear, it can be speculated that increased IC/TLC in obese patients with COPD [78] may contribute to a benefit in survival. In addition, obesity is associated with significantly lower annual decline in FEV₁ in males but not in females [88]. Thus, there may be sex-specific differences in the effect of obesity on the progression of chronic airflow limitation. Furthermore, it is not yet clear whether excessive fat mass or muscle mass contributes to the survival advantage in chronic diseases [86].

Based on the evidence outlined above, it can be hypothesised that obesity exerts divergent effects on COPD prognosis based on patient characteristics and disease severity. Obesity may protect against mortality in advanced COPD patients, in which loss of fat-free mass is a particularly important short-term risk factor for death [20]. By contrast, in earlier stage COPD, the harmful long-term effects of obesity-related conditions such as low-grade systemic inflammation and metabolic syndrome may result in increased cardiovascular and all-cause mortality.

Metabolic syndrome in COPD

Patients with COPD are at high risk of hospitalisation and death from cardiovascular disease [89] and at increased risk of diabetes [90]. Although the mechanisms responsible for this association remain largely unknown, obesity is associated with abnormal metabolic and inflammatory responses that may contribute to increased cardiovascular morbidity in COPD.

Metabolic syndrome is a cluster of risk factors (*i.e.* hypertension, dyslipidaemia and diabetes) for cardiovascular disease [91]. Central obesity is one of the key factors in the pathogenesis of this syndrome, in addition to physical inactivity, nutrition, ageing, genetics, a pro-inflammatory state and hormonal changes [92]. Metabolic syndrome is associated with restrictive lung function impairment, independent of waist circumference and BMI [93]. In a large population-based study, the risk of metabolic syndrome was 40% higher in subjects with restrictive lung function

impairment compared to subjects with normal lung function [94]. Abdominal obesity, not BMI, was the strongest predictor of lung function impairment in that study.

Several studies have investigated the prevalence of metabolic syndrome in patients with COPD. In a small study of patients with severe COPD referred for pulmonary rehabilitation, 47% of patients fulfilled the diagnostic criteria for metabolic syndrome. This percentage was significantly higher compared to the age- and sex-matched control subjects, in whom the prevalence of metabolic syndrome was only 21% [95]. Similar results were reported in a larger study including patients with chronic bronchitis and COPD [96]. Although the prevalence of metabolic syndrome does not appear to vary based on the severity of lung disease, it is associated with increased circulatory levels of high-sensitivity (hs)CRP and interleukin (IL)-6 and with physical inactivity. These associations were independent of lung function impairment [96]. Future studies should focus on whether patients with COPD and metabolic syndrome have an increased risk of developing comorbidities including cardiovascular diseases and diabetes and whether this contributes to increased cardiovascular and all-cause mortality in these patients.

Systemic inflammation

Low-grade systemic inflammation is considered a hallmark of COPD [97, 98] and may explain the increased cardiovascular morbidity and metabolic syndrome noted in patients with COPD. Indeed, increased levels of pro-inflammatory cells and mediators have been reported in the circulation of COPD patients, including increased plasma concentrations of fibrinogen, CRP, tumour necrosis factor (TNF)- α and circulating leukocytes [97]. Increased levels of IL-6 [99, 100], IL-8 [101], IL-10 [99] and IL-18 [102] have also been reported. Although it is often hypothesised that inflammation in the systemic compartment is the result of spill-over of the inflammatory process in the airways, lung parenchyma and pulmonary vasculature, evidence from cross-sectional studies indicates no correlation between pulmonary and circulatory inflammatory markers in stable COPD [101, 103]. In addition, it is becoming more and more evident that systemic inflammation is not a characteristic of all patients with COPD. In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study, only 16% of patients had persistent systemic inflammation during follow-up [104]. Interestingly, patients with systemic inflammation were more obese, and had more respiratory symptoms, lower health-related quality of life, worse exercise tolerance and reported more cardiovascular disease [104]. The ECLIPSE data suggest a systemic origin of inflammation and are in line with previous observations suggesting that adipose tissue is a potential source. Increased levels of systemic inflammation have been previously reported in relation to excessive fat mass in COPD patients. Specifically, TNF- α , IL-6 and leptin plasma levels have been shown to be significantly increased in overweight/obese patients compared with normal weight patients, while plasma adiponectin concentrations were reduced [98]. The likelihood of having elevated CRP is three times higher in obese patients compared to normal-weight patients, after adjusting for relevant confounders [105], with abdominal fat mass being positively associated with plasma CRP levels in patients with COPD [56].

Few studies examined adipose tissue inflammation in COPD. Significant differences in subcutaneous adipose tissue mRNA expression of pro-inflammatory IL-6, TNF- α and CD68 (macrophage cell surface receptor) were reported among cachectic, normal weight, overweight and obese patients with moderate-to-severe COPD [106]. However, there was no difference in serum levels of IL-6, TNF- α and hsCRP [106]. In another study, gene expression of pro-inflammatory CD40, mitogen-activated protein kinase (MKK)-4 and c-Jun NH₂-terminal kinases (JNK) was increased in subcutaneous adipose tissue in underweight and muscle-wasted COPD patients with resting hypoxia, compared to less severe patients with overweight and preserved muscle mass [107]. Upregulation of CD40, MKK4 and JNK was inversely related to arterial oxygen tension (P_{a,O_2}), BMI and adipocyte diameter. However, since no healthy control groups matched for body composition were included, a COPD-specific effect on adipose tissue inflammation could not be assessed. Furthermore, given comparable levels of circulating hsCRP and IL-6 levels in the

underweight hypoxaemic patients and the overweight normoxaemic patients, a link between white adipose tissue inflammation and systemic inflammation could not be proven. Recently, comparable adipokine and inflammatory gene expression was reported in subcutaneous adipose tissue of clinically stable, normal weight COPD patients and matched controls [108]. Also, adipocyte size, adipose tissue macrophage infiltration and systemic adipokine concentrations were comparable. However, independent of body composition, COPD patients with high CRP had significantly greater adipose tissue macrophage infiltration than patients with low CRP, indicating a possible role of adipose tissue macrophages in the pathophysiology of systemic inflammation in COPD. In conclusion, specific alterations in adipose tissue function in patients with concomitant COPD and obesity currently remain unknown. The impact of fat mass distribution (*i.e.* subcutaneous *versus* visceral fat mass or abdominal *versus* lower-extremity fat mass) on systemic inflammation in COPD may be explored in future studies.

Pulmonary rehabilitation

Pulmonary rehabilitation has been shown to improve symptoms, exercise tolerance, body composition and health status in patients with COPD in general [109]. Given these beneficial effects, pulmonary rehabilitation seems to be a useful adjunct in the comprehensive management of patients with COPD as well as obesity. However, few studies addressed the effects of pulmonary rehabilitation in this patient category. In a retrospective study, similar improvements in 6-minute walking distance, health status and functional activities (using the pulmonary functional status scale) were observed in obese and non-obese COPD patients after an outpatient pulmonary rehabilitation programme [75]. However, obese patients improved less in unsupported arm exercise than non-obese patients [75]. In another study, the magnitude of improvement in walking distance, cycling endurance time and health status after pulmonary rehabilitation was also comparable in normal weight, overweight and obese COPD patients [110]. No significant changes in BMI were noticed after pulmonary rehabilitation [110]. Given the impact of obesity on weight-bearing exercise performance in patients with COPD [78], the ability to perform traditional exercise training may be limited. Water-based exercise training may provide an alternative mode of training for these patients with concurrent COPD and obesity. In a recent study, including not only COPD patients with obesity but also with other musculoskeletal comorbidities limiting exercise capacity, water-based exercise training was more effective than land-based exercise training in increasing peak and endurance exercise capacity and improving symptoms of fatigue [111]. Changes in body weight were not reported. Based on these limited studies, it appears that obesity *per se* does not have a negative impact on the outcomes of pulmonary rehabilitation in patients with COPD. To date, no studies focussed on optimisation of nutritional and lifestyle interventions as part of pulmonary rehabilitation in obese COPD patients, in which losing excess fat may be an important goal. Studying the impact of weight reduction strategies in conjunction with exercise training in this specific patient population should be a research priority.

Conclusion

From the present research it is clear that malnutrition is present more often in patients with COPD than in the elderly without coexisting COPD, and that it contributes to the complexity of the disease and to a worse prognosis. Various disease-specific factors can contribute to the development of malnutrition in COPD including medication use, hypoxia, exacerbation rate and physical inactivity. Nevertheless, the progressive decline of the muscle mass is not disease specific *per se*, and more longitudinal research is warranted to unravel the phenotype of COPD specified by a thin body shape. However, as weight loss is associated with worse survival, clinicians should be aware of involuntary weight loss besides assessment of body composition when screening patients with COPD.

However, COPD and obesity are two heterogeneous chronic conditions with increasing prevalence worldwide. In COPD, obesity results in reductions in static lung hyperinflation, irrespective of the

severity of airflow limitation. The impact of obesity on exercise capacity in COPD is probably dependent on the type of exercise. It is currently unknown whether and to what extent adipose tissue dysfunction and insulin resistance contribute to increased cardiovascular risk and extra pulmonary manifestations in COPD. In contrast to early stage COPD, obesity seems to protect against mortality in patients with severe disease. Even though additional studies on the interaction between obesity and COPD are warranted, the current findings suggest that the presence of obesity has implications for the interpretation of diagnostic measurements and management of patients with COPD.

Statement of Interest

None declared.

References

1. Filley GF, Beckwith HJ, Reeves JT, *et al.* Chronic obstructive bronchopulmonary disease. II. Oxygen transport in two clinical types. *Am J Med* 1968; 44: 26–38.
2. Beers MH, Berkow R. Malnutrition. In: Whitehouse Station NMRL, ed. The Merck Manual of Diagnosis and Therapy. New York, Merck Research Laboratories, 2004.
3. Schols AM, Wouters EF, Soeters PB, *et al.* Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 1991; 53: 421–424.
4. King DA, Cordova F, Scharf SM. Nutritional aspects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 519–523.
5. Schols AMWJ, Mostert R, Cobben N, *et al.* Transcutaneous oxygen saturation and carbon dioxide tension during meals in patients with chronic obstructive pulmonary disease. *Chest* 1991; 100: 1287–1292.
6. de Batlle J, Romieu I, Anto JM, *et al.* Dietary habits of firstly admitted Spanish COPD patients. *Respir Med* 2009; 103: 1904–1910.
7. Franssen FM, Wouters EF, Baarends EM, *et al.* Arm mechanical efficiency and arm exercise capacity are relatively preserved in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2002; 34: 1570–1576.
8. Sergi G, Coin A, Marin S, *et al.* Body composition and resting energy expenditure in elderly male patients with chronic obstructive pulmonary disease. *Respir Med* 2006; 100: 1918–1924.
9. Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. *Chest* 2003; 123: 1460–1466.
10. Landbo C, Prescott E, Lange P, *et al.* Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856–1861.
11. Lainscak M, von Haehling S, Doehner W, *et al.* Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *J Cachex Sarcopenia Muscle* 2011; 2: 81–86.
12. Celli BR, Cote CG, Marin JM, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
13. Schols AMWJ, Soeters PB, Dingemans AMC, *et al.* Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993; 147: 1151–1156.
14. Budweiser S, Meyer K, Jorres RA, *et al.* Nutritional depletion and its relationship to respiratory impairment in patients with chronic respiratory failure due to COPD or restrictive thoracic diseases. *Eur J Clin Nutr* 2008; 62: 436–443.
15. Schols AM, Mostert R, Soeters PB, *et al.* Body composition and exercise performance in patients with chronic obstructive pulmonary disease. *Thorax* 1991; 46: 695–699.
16. Bernard S, LeBlanc P, Whittom F, *et al.* Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 629–634.
17. Mostert R, Goris A, Weling-Scheepers C, *et al.* Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 2000; 94: 859–867.
18. Ferrari R, Tanni SE, Faganello MM, *et al.* Three-year follow-up study of respiratory and systemic manifestations of chronic obstructive pulmonary disease. *Braz J Med Biol Res* 2011; 44: 46–52.
19. Vestbo J. Clinical assessment, staging, and epidemiology of chronic obstructive pulmonary disease exacerbations. *Proc Am Thorac Soc* 2006; 3: 252–256.
20. Schols AM, Broekhuizen R, Weling-Scheepers CA, *et al.* Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005; 82: 53–59.
21. Vermeeren MA, Creutzberg EC, Schols AM, *et al.* Prevalence of nutritional depletion in a large out-patient population of patients with COPD. *Respir Med* 2006; 100: 1349–1355.
22. Vestbo J, Prescott E, Almdal T, *et al.* Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 2006; 173: 79–83.

23. Steuten LM, Creutzberg EC, Vrijhoef HJ, *et al.* COPD as a multicomponent disease: inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care. *Prim Care Respir J* 2006; 15: 84–91.
24. Laaban JP, Kouchakji B, Dore MF, *et al.* Nutritional status of patients with chronic obstructive pulmonary disease and acute respiratory failure. *Chest* 1993; 103: 1362–1368.
25. Rutten EP, Bakke P, Sreekumar GP, *et al.* The association between body composition and self-reported co-morbidity in subjects with chronic obstructive pulmonary disease. *Open J Int Med* 2012; 2: 100–106.
26. van den Borst B, Koster A, Yu B, *et al.* Is age-related decline in lean mass and physical function accelerated by obstructive lung disease or smoking? *Thorax* 2011; 66: 961–969.
27. Eliason G, Abdel-Halim SM, Piehl-Aulin K, *et al.* Alterations in the muscle-to-capillary interface in patients with different degrees of chronic obstructive pulmonary disease. *Respir Res* 2010; 11: 97.
28. Whittom F, Jobin J, Simard PM, *et al.* Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1998; 30: 1467–1474.
29. Gosker HR, van Mameren H, van Dijk PJ, *et al.* Skeletal muscle fibre-type shifting and metabolic profile in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 617–625.
30. Gosker H, Zeegers M, Wouters E, *et al.* Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax* 2007; 62: 944–949.
31. Shrikrishna D, Patel M, Tanner RJ, *et al.* Quadriceps wasting and physical inactivity in patients with COPD. *Eur Respir J* 2012; 40: 1115–1122.
32. Engelen MP, Deutz NE, Wouters EF, *et al.* Enhanced levels of whole-body protein turnover in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1488–1492.
33. Rutten EP, Franssen FM, Engelen MP, *et al.* Greater whole-body myofibrillar protein breakdown in cachectic patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 2006; 83: 829–834.
34. Bolton CE, Broekhuizen R, Ionescu AA, *et al.* Cellular protein breakdown and systemic inflammation are unaffected by pulmonary rehabilitation in COPD. *Thorax* 2007; 62: 109–114.
35. Broekhuizen R, Grimble RF, Howell WM, *et al.* Pulmonary cachexia, systemic inflammatory profile, and the interleukin 1 β -511 single nucleotide polymorphism. *Am J Clin Nutr* 2005; 82: 1059–1064.
36. Hofford JM, Milakofsky L, Vogel WH, *et al.* The nutritional status in advanced emphysema associated with chronic bronchitis. A study of amino acid and catecholamine levels. *Am Rev Respir Dis* 1990; 141: 902–908.
37. Morrison WL, Gibson JNA, Scrimgeour C, *et al.* Muscle wasting in emphysema. *Clin Sci* 1988; 75: 415–420.
38. Schols AMWJ, Deutz NEP, Mostert R, *et al.* Plasma amino acid levels in patients with chronic obstructive pulmonary disease. *Monaldi Arch Chest Med* 1993; 48: 546–548.
39. Engelen MP, Wouters EF, Deutz NE, *et al.* Factors contributing to alterations in skeletal muscle and plasma amino acid profiles in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 2000; 72: 1480–1487.
40. Franssen FM, Sauerwein HP, Ackermans MT, *et al.* Increased post absorptive and exercise-induced whole-body glucose production in patients with chronic obstructive pulmonary disease. *Metabolism* 2011; 60: 957–964.
41. Murton AJ, Constantin D, Greenhaff PL. The involvement of the ubiquitin proteasome system in human skeletal muscle remodelling and atrophy. *Biochim Biophys Acta* 2008; 1782: 730–743.
42. Langen RC, Van Der Velden JL, Schols AM, *et al.* Tumor necrosis factor- α inhibits myogenic differentiation through MyoD protein destabilization. *FASEB J* 2004; 18: 227–237.
43. Doucet M, Russell AP, Leger B, *et al.* Muscle atrophy and hypertrophy signalling in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 261–269.
44. Faner R, Rojas M, Macnee W, *et al.* Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012; 186: 306–313.
45. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest* 2009; 135: 173–180.
46. Pitta F, Troosters T, Spruit MA, *et al.* Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 972–977.
47. Hopkinson NS, Tennant RC, Dayer MJ, *et al.* A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. *Respir Res* 2007; 8: 25.
48. Decramer M, Lacquet LM, Fagard R, *et al.* Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994; 150: 11–16.
49. Raguso CA, Luthy C. Nutritional status in chronic obstructive pulmonary disease: role of hypoxia. *Nutrition* 2011; 27: 138–143.
50. Davidson AC, Leach R, George RJ, *et al.* Supplemental oxygen and exercise ability in chronic obstructive airways disease. *Thorax* 1988; 43: 965–971.
51. Glass DJ. Skeletal muscle hypertrophy and atrophy signaling pathways. *Int J Biochem Cell Biol* 2005; 37: 1974–1984.
52. Remels AH, Gosker HR, Schrauwen P, *et al.* TNF- α impairs regulation of muscle oxidative phenotype: implications for cachexia? *FASEB J* 2010; 24: 5052–5062.
53. Langen RC, Schols AM, Kelders MC, *et al.* Muscle wasting and impaired muscle regeneration in a murine model of chronic pulmonary inflammation. *Am J Respir Cell Mol Biol* 2006; 35: 689–696.
54. Langen RC, Haegens A, Vernooij JH, *et al.* NF- κ B activation is required for the transition of pulmonary inflammation to muscle atrophy. *Am J Respir Cell Mol Biol* 2012; 47: 288–297.
55. Eagan TM, Gabazza EC, D'Alessandro-Gabazza C, *et al.* TNF- α is associated with loss of lean body mass only in already cachectic COPD patients. *Respir Res* 2012; 13: 48.

56. Rutten EP, Breyer MK, Spruit MA, *et al.* Abdominal fat mass contributes to the systemic inflammation in chronic obstructive pulmonary disease. *Clin Nutr* 2010; 29: 756–760.
57. Eagan TM, Aukrust P, Ueland T, *et al.* Body composition and plasma levels of inflammatory biomarkers in COPD. *Eur Respir J* 2010; 36: 1027–1033.
58. Lamprecht B, McBurnie MA, Vollmer WM, *et al.* COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 2011; 139: 752–763.
59. Prescott E, Almdal T, Mikkelsen KL, *et al.* Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. *Eur Respir J* 2002; 20: 539–544.
60. Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Am J Clin Nutr* 2012; 95: 1385–1395.
61. Ferreira IM, Brooks D, Lacasse Y, *et al.* Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 2: CD000998.
62. Sugawara K, Takahashi H, Kasai C, *et al.* Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir Med* 2010; 104: 1883–1889.
63. Sugawara K, Takahashi H, Kashiwagura T, *et al.* Effect of anti-inflammatory supplementation with whey peptide and exercise therapy in patients with COPD. *Respir Med* 2012; 106: 1526–1534.
64. van Wetering CR, Hoogendoorn M, Mol SM, *et al.* Short- and long-term efficacy of a community-based COPD management program in less advanced COPD: a randomized controlled trial. *Thorax* 2010; 65: 7–13.
65. Puhan M, Scharplatz M, Troosters T, *et al.* Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009; 1: CD005305.
66. van Wetering CR, Hoogendoorn M, Broekhuizen R, *et al.* Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. *J Am Med Dir Assoc* 2010; 11: 179–187.
67. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. *World Health Organ Tech Rep Ser* 2000; 894: 1–253.
68. Vozoris NT, O'Donnell DE. Prevalence, risk factors, activity limitation and health care utilization of an obese, population-based sample with chronic obstructive pulmonary disease. *Can Respir J* 2012; 19: e18–e24.
69. Eisner MD, Blanc PD, Sidney S, *et al.* Body composition and functional limitation in COPD. *Respir Res* 2007; 8: 7.
70. Montes de Oca M, Talamo C, Perez-Padilla R, *et al.* Chronic obstructive pulmonary disease and body mass index in five Latin America cities: the PLATINO study. *Respir Med* 2008; 102: 642–650.
71. Schokker DF, Visscher TL, Nooyens AC, *et al.* Prevalence of overweight and obesity in the Netherlands. *Obes Rev* 2007; 8: 101–108.
72. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. *Arch Intern Med* 2002; 162: 1477–1481.
73. Zutler M, Singer JP, Omachi TA, *et al.* Relationship of obesity with respiratory symptoms and decreased functional capacity in adults without established COPD. *Prim Care Respir J* 2012; 21: 194–201.
74. Cecere LM, Littman AJ, Latore CG, *et al.* Obesity and COPD: associated symptoms, health-related quality of life, and medication use. *COPD* 2011; 8: 275–284.
75. Ramachandran K, McCusker C, Connors M, *et al.* The influence of obesity on pulmonary rehabilitation outcomes in patients with COPD. *Chron Respir Dis* 2008; 5: 205–209.
76. Pelosi P, Croci M, Ravagnan I, *et al.* Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. *Chest* 1996; 109: 144–151.
77. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol* 2010; 108: 206–211.
78. Ora J, Laveneziana P, Ofir D, *et al.* Combined effects of obesity and chronic obstructive pulmonary disease on dyspnea and exercise tolerance. *Am J Respir Crit Care Med* 2009; 180: 964–971.
79. O'Donnell DE, Deesomchok A, Lam YM, *et al.* Effects of body mass index on static lung volumes in patients with airway obstruction. *Chest* 2011; 140: 461–468.
80. Babb TG, Ransinghe KG, Comeau LA, *et al.* Dyspnea on exertion in obese women: association with an increased oxygen cost of breathing. *Am J Respir Crit Care Med* 2008; 178: 116–123.
81. Bautista J, Ehsan M, Normandin E, *et al.* Physiologic responses during the six minute walk test in obese and non-obese COPD patients. *Respir Med* 2011; 105: 1189–1194.
82. Peeters A, Barendregt JJ, Willekens F, *et al.* Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Med* 2003; 138: 24–32.
83. Whitlock G, Lewington S, Sherliker P, *et al.* Body-mass index and cause-specific mortality in 900000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; 373: 1083–1096.
84. Schols AMWJ, Slangen J, Volovics L, *et al.* Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791–1797.
85. Wilson DO, Rogers RM, Wright EC, *et al.* Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989; 139: 1435–1438.
86. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, *et al.* Risk factor paradox in wasting diseases. *Curr Opin Clin Nutr Metab Care* 2007; 10: 433–442.

87. Casanova C, Cote C, de Torres JP, *et al.* Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 591–597.
88. Watson L, Vonk JM, Lofdahl CG, *et al.* Predictors of lung function and its decline in mild to moderate COPD in association with gender: results from the Euroscop study. *Respir Med* 2006; 100: 746–753.
89. Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962–969.
90. Feary JR, Rodrigues LC, Smith CJ, *et al.* Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010; 65: 956–962.
91. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; 366: 1059–1062.
92. Huang TT, Ball GD, Franks PW. Metabolic syndrome in youth: current issues and challenges. *Appl Physiol Nutr Metab* 2007; 32: 13–22.
93. Fimognari FL, Pasqualetti P, Moro L, *et al.* The association between metabolic syndrome and restrictive ventilatory dysfunction in older persons. *J Gerontol A Biol Sci Med Sci* 2007; 62: 760–765.
94. Leone N, Courbon D, Thomas F, *et al.* Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009; 179: 509–516.
95. Marquis K, Maltais F, Duguay V, *et al.* The metabolic syndrome in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2005; 25: 226–232.
96. Watz H, Waschki B, Kirsten A, *et al.* The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009; 136: 1039–1046.
97. Gan WQ, Man SF, Senthilselvan A, *et al.* Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574–580.
98. Poulain M, Doucet M, Drapeau V, *et al.* Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. *Chron Respir Dis* 2008; 5: 35–41.
99. Koehler F, Doehner W, Hoernig S, *et al.* Anorexia in chronic obstructive pulmonary disease - association to cachexia and hormonal derangement. *Int J Cardiol* 2007; 119: 83–89.
100. Yasuda N, Gotoh K, Minatoguchi S, *et al.* An increase of soluble Fas, an inhibitor of apoptosis, associated with progression of COPD. *Respir Med* 1998; 92: 993–999.
101. Vernooy JH, Kucukaycan M, Jacobs JA, *et al.* Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. *Am J Respir Crit Care Med* 2002; 166: 1218–1224.
102. Petersen AM, Penkowa M, Iversen M, *et al.* Elevated levels of IL-18 in plasma and skeletal muscle in chronic obstructive pulmonary disease. *Lung* 2007; 185: 161–171.
103. Donaldson GC, Seemungal TA, Patel IS, *et al.* Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest* 2005; 128: 1995–2004.
104. Agusti A, Edwards LD, Rennard SI, *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7: e37483.
105. Breyer MK, Spruit MA, Celis AP, *et al.* Highly elevated C-reactive protein levels in obese patients with COPD: a fat chance? *Clin Nutr* 2009; 28: 642–647.
106. Skyba P, Ukropec J, Pobeha P, *et al.* Metabolic phenotype and adipose tissue inflammation in patients with chronic obstructive pulmonary disease. *Mediators Inflamm* 2010; 2010: 173498.
107. Tkacova R, Ukropec J, Skyba P, *et al.* Increased adipose tissue expression of proinflammatory CD40, MKK4 and JNK in patients with very severe chronic obstructive pulmonary disease. *Respiration* 2010; 81: 386–393.
108. van den Borst B, Gosker HR, Wesseling G, *et al.* Low-grade adipose tissue inflammation in patients with mild-to-moderate chronic obstructive pulmonary disease. *Am J Clin Nutr* 2011; 94: 1504–1512.
109. Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.
110. Sava F, Laviolette L, Bernard S, *et al.* The impact of obesity on walking and cycling performance and response to pulmonary rehabilitation in COPD. *BMC Pulm Med* 2010; 10: 55.
111. McNamara RJ, McKeough ZJ, McKenzie DK, *et al.* Water-based exercise in COPD with physical co-morbidities: a randomised controlled trial. *Eur Respir J* [Epub ahead of print DOI: 10.1183/09031936.00034312].

Chapter 7

Osteoporosis in COPD

Elisabeth A.P.M. Romme*, Frank W.J.M. Smeenk*,
Emiel F.M. Wouters[#] and Erica P.A. Rutten[†]



SUMMARY: COPD is, in addition to progressive airflow obstruction, characterised by extrapulmonary manifestations that contribute to the disease severity in individual patients. Osteoporosis is recognised as one such extrapulmonary manifestation, since the prevalence of osteoporosis is higher in COPD patients than in control subjects matched for age and sex. Osteoporosis is a skeletal disease characterised by low bone mineral density or micro-architectural deterioration, resulting in increased risk of fracture. The high prevalence of osteoporosis in COPD is probably due to common risk factors such as advanced age and smoking, and to COPD-specific risk factors such as systemic inflammation and the use of corticosteroids. Interventions against common risk factors, like smoking cessation, exercise and healthy diet, might reduce the risk of fracture in patients with osteoporosis. In addition to these lifestyle guidelines, pharmacological treatment with calcium and vitamin D supplementation and antiresorptive treatment (e.g. bisphosphonates) have been indicated to prevent fractures in patients with osteoporosis.

KEYWORDS: Bone density, comorbidity, COPD, osteoporosis, vitamin D

*Dept of Respiratory Medicine, Catharina Hospital, Eindhoven,
[#]Dept of Respiratory Medicine, Maastricht University Medical Centre, Maastricht University, Maastricht, and
[†]Program Development Centre, Centre of Expertise for Chronic Organ failure (CIRO⁺), Horn, The Netherlands.

Correspondence: E.A.P.M. Romme, Dept of Respiratory Medicine, Catharina Hospital, P.O. Box 1350, 5602 ZA Eindhoven, The Netherlands. Email: lisette.romme@catharinaziekenhuis.nl

Eur Respir Monogr 2013; 59: 93–104.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011712
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Osteoporosis is recognised as an extrapulmonary manifestation of COPD that might contribute to morbidity and mortality in COPD [1]. In this chapter, we will provide an overview of the prevalence, risk factors and treatment of osteoporosis in patients with COPD.

Osteoporosis

Osteoporosis is a systemic skeletal disease that is characterised by low bone mineral density or micro-architectural deterioration, resulting in bone fragility and hence increased risk of fracture [2]. Osteoporotic fractures may cause significant morbidity and mortality, particularly in patients with COPD, in whom vertebral compression fractures may reduce already compromised pulmonary function [1, 3]. Moreover, COPD results in a higher operation risk for hip surgery after osteoporosis related fractures [4].

At present, the gold standard to diagnose osteoporosis is dual energy X-ray absorptiometry (DXA). The World Health Organisation (WHO) [2] and the International Society for Clinical Densitometry [5] recommend a diagnosis of osteoporosis based on the lowest T-score of the hip or

Table 1. Diagnosis of osteoporosis

	T-score
Normal bone mass	≥ -1.0
Osteopenia	-1.0 to -2.5
Osteoporosis	≤ -2.5

assessment on radiographs of the spine has been recommended in patients with moderate-to-very-severe COPD [5], since vertebral fractures are highly prevalent in COPD [6] and related to a high annual number of incidental vertebral fractures [7]. The clinical technique of choice for diagnosing vertebral fracture is the visual semi-quantitative method of GENANT *et al.* [8]. With this method, vertebral deformities are classified into wedge, biconcave or crush and into grade 1 (20–25% reduction in height and 10–20% reduction of the projected vertebral area), grade 2 (25–40% reduction in height and 20–40% reduction of the projected vertebral area) and grade 3 (>40% reduction in height and area).

Pathophysiology of osteoporosis

Bone is generally classified into two types: 1) cortical bone, which is dense and strong and primarily present in the shafts of long bones; and 2) trabecular bone, which is weak and porous and present at the ends of long bones or at the interior of vertebrae and flat bones. Bone tissue is continuously renewed throughout life and it is estimated that about 25% of trabecular bone and about 3% of cortical bone is replaced in adults every year.

Osteoporosis can occur because of a failure to achieve peak bone mass, or it can be due to excessive bone resorption and decreased bone formation during bone remodelling. Bone remodelling is a complex interplay between osteoblasts, osteoclasts and osteocytes. These cells remove an area of bone and then replace the lost bone with new matrix which subsequently mineralises. Excessive bone resorption, due to an imbalance in the amount of bone removed relative to the amount of bone replaced, will lead to a decline in the total amount of bone and will increase the risk of fracture.

Bone remodelling is controlled by several mechanisms such as the osteoprotegerin (OPG)/receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANKL) system and the Wnt/ β -catenin signalling pathway (fig. 1). RANKL is expressed on the surface of osteoblasts, and its expression increases in response to a variety of pro-resorptive signals, such as parathyroid hormone (PTH) and inflammatory cytokines. RANKL binds to the RANK receptor, which is expressed on osteoclasts and their precursors, thereby stimulating the differentiation and activation of osteoclasts and hence

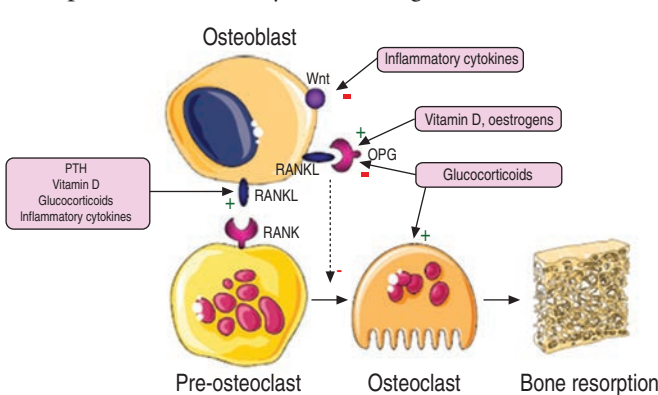


Figure 1. Key mechanisms in the pathogenesis of osteoporosis in COPD. RANK: receptor activator of nuclear factor- κ B; RANKL: RANK ligand; OPG: osteoprotegerin; PTH: parathyroid hormone. Reproduced and modified from [9] with permission from the publisher.

the lumbar spine measured on DXA (table 1). The T-score is defined as the number of standard deviations by which the bone mineral density differs from the average bone mineral density of a young adult at peak bone density.

In addition to DXA scanning, vertebral fracture assessment on radiographs of the spine has been recommended in patients with moderate-to-very-severe COPD [5], since vertebral fractures are highly prevalent in COPD [6] and related to a high annual number of incidental vertebral fractures [7]. The clinical technique of choice for diagnosing vertebral fracture is the visual semi-quantitative method of GENANT *et al.* [8]. With this method, vertebral deformities are classified into wedge, biconcave or crush and into grade 1 (20–25% reduction in height and 10–20% reduction of the projected vertebral area), grade 2 (25–40% reduction in height and 20–40% reduction of the projected vertebral area) and grade 3 (>40% reduction in height and area).

promoting bone resorption. OPG is a decoy receptor for RANKL that is secreted by osteoblasts and other stroma-derived cells and acts to reduce bone resorption. Imbalance between RANKL and OPG results in excessive activity of osteoclasts and is considered a major cause of osteoporosis. The Wnt/ β -catenin signalling pathway is less well understood, but it is known that it has an important role in bone formation by activating osteoblasts. Wnt inhibitors, such as inflammatory cytokines, negatively regulate this pathway resulting in bone loss [1, 10].

Prevalence of osteoporosis in COPD

The prevalence of osteoporosis is high in patients with COPD. In the TORCH (Towards a Revolution in COPD Health) study, which included 658 COPD patients, 23% had osteoporosis and 43% had osteopenia at the hip or the lumbar spine on DXA according to the WHO guidelines [9]. This is in line with another study on 255 COPD patients admitted for pulmonary rehabilitation, 24% of whom had osteoporosis and 46% had osteopenia [11]. When taking the vertebral fractures into account, the prevalence of osteoporosis even increased to 51% [11].

Smaller studies have demonstrated that the prevalence of osteoporosis is higher in patients with COPD than in healthy control subjects. In a group of 81 COPD patients and 38 sex-matched controls, 30% of the COPD patients and 13% of the controls had osteoporosis [12]. However, in this study the controls were younger than the COPD patients. Nevertheless, in a more recent study the prevalence of osteoporosis was 24% in COPD patients and 5% in controls matched for age and sex [13]. Although large case-control studies are not yet available, the available data suggest a higher prevalence of osteoporosis among patients with COPD than in subjects without coexisting COPD.

Risk factors of osteoporosis in COPD

In healthy males and females, the main risk factors for osteoporosis are advanced age, smoking, low body weight, physical inactivity, prevalent fractures after the age of 50 years and post-menopausal status [14, 15]. A collection of these risk factors is summarised in the fracture risk assessment tool, which predicts the 10-year probability of fracture [16]. Since some of these risk factors like advanced age, smoking and low body weight coincide in patients with COPD, it is not surprising that osteoporosis and COPD are strongly related. However, there is evidence that various COPD-specific factors such as systemic inflammation, vitamin D deficiency, use of corticosteroids and lung function impairment themselves might contribute to the increased risk of osteoporosis in patients with COPD. In the following paragraphs, we will discuss the most important risk factors of osteoporosis in patients with COPD.

Airflow obstruction and emphysema

Osteoporosis has been related to severity of airflow obstruction. The third National Health and Nutrition Examination Survey, which included 9,502 participants, showed that the prevalence of osteopenia and osteoporosis increased with more severe airflow obstruction [17]. In line with this, in 4,830 females recruited from general practice registers, forced expiratory volume in 1 second (FEV₁) was positively correlated with bone mineral density after adjustment for confounders, including *e.g.* corticosteroid use [18]. More recently, a cross-sectional study with 95 COPD patients demonstrated that the patients with osteoporosis had lower FEV₁ than the patients with normal bone mass [19]. In line with this, a review stated that osteoporosis was associated with more severe airflow obstruction in patients with COPD [20]. In contrast, some studies on patients with COPD did not find a relationship between bone mineral density and severity of airflow obstruction after correction for confounders [21, 22].

In addition to its association with severity of airflow obstruction, bone density has been related to the extent of emphysema [23]. In 1999, a study in approximately 100 patients with severe COPD who had been admitted for pulmonary rehabilitation showed that total body bone mineral density was lower in the patients with emphysema, based on visual scores on high-resolution computed tomography (HRCT) scans, than in those without emphysema [24]. BON *et al.* [25] recently confirmed these data in a tobacco-exposed cohort of which only a subset of subjects had obstructive lung disease. They showed that radiographic emphysema was an independent predictor of low bone mineral density. However, they did not correct for body mass index (BMI), even though BMI is related to both emphysema and bone mineral density. However, in another study on 65 male patients with COPD, radiographic emphysema was correlated with computed

tomography (CT)-measured bone mineral density of the thoracic vertebrae even after adjustment for BMI [26].

Since bone mineral density was shown to be correlated independently with both the severity of airflow obstruction and the extent of emphysema, recent research has been focused on common links between the skeletal and pulmonary systems [23]. Both direct and indirect pathways have been suggested.

Regarding the indirect pathways, COPD is associated with increased plasma markers of systemic inflammation that might stimulate osteoclastogenesis and generate RANKL, resulting in decreased bone mass. In a clinical study with 80 subjects, plasma markers of systemic inflammation, interleukin (IL)-6 and tumour necrosis factor (TNF)- α were higher in the COPD patients than in the control subjects and higher in the COPD patients with low bone density than in the COPD patients with normal bone density [27]. In addition, the RANKL concentration and the RANKL/OPG ratio were higher in the COPD patients with low bone density than in the COPD patients with normal bone density. Therefore, it seems likely that systemic inflammation in COPD results in a disturbance of the RANK/RANKL/OPG pathway and, hence, in osteoporosis. A review stated that systemic inflammation might result in disturbance of the RANK/RANKL/OPG pathway in patients with inflammatory diseases [9].

Regarding the direct pathways, the Wnt/ β -catenin signalling is involved in bone remodelling and repair of micro-fractures, but it has also been associated with lung epithelial injury and repair processes. In a small study with 12 COPD and 12 transplant donor lung samples, Wnt/ β -catenin activation by lithium chloride attenuated experimental emphysema as assessed by decreased airspace enlargement, improved lung function, reduced collagen content and elevated expression of alveolar epithelial cell markers [28]. Therefore, it might be the case that impairment of Wnt/ β -catenin signalling results in both osteoporosis and emphysema. However, only indirect and experimental evidence supporting this interaction is available to date.

Ageing

Advanced age is a well-established risk factor for osteoporosis [2, 16] and has been related to the presence of COPD in a large population-based cohort study [29]. COPD has even been suggested to be a syndrome of abnormal lung ageing [30]. Since patients with COPD show evidence of increased oxidative stress [31] and shorter telomeres compared with controls matched for age and sex [32], there seems to be evidence that COPD is also associated with systemic abnormal ageing [33].

The underlying patho-physiological mechanism of the relationship between advanced age and bone loss has been widely studied [34]. In a healthy young skeleton the rate of bone formation and matrix mineralisation equals the rate of bone resorption and matrix degradation. However, during the process of ageing significant amounts of bone are lost due to enhanced bone resorption coupled with decreased bone formation. In addition to bone loss, advanced age is associated with increased fall risk due to muscle weakness and balance disorders resulting in increased risk of fracture [35, 36].

Body composition

Low body mass/fat-free mass

Low body mass and low fat-free mass are well-known risk factors for osteoporosis in the general population [2, 16]. Moreover, low body mass and low fat-free mass are both commonly present and have been investigated extensively in patients with COPD as they are associated with decreased exercise tolerance [37], disease-related quality of life [38] and increased mortality risk [39]. In addition, accumulating evidence shows a relationship between low body and muscle mass and osteoporosis in patients with COPD even after adjustment for confounders such as age and the use of corticosteroids [12, 20–22, 40].

Low body mass, low fat-free mass and the poor exercise capacity related to it might induce bone loss due to decreased mechanical loading [37]. Indeed, astronauts lose bone mass in the proximal femur during space flights [41], and long-term bed rest leads to loss of bone mass [42]. Although “disuse” osteoporosis has been investigated widely [43], its underlying mechanism is not yet fully understood. In addition to decreased mechanical loading, poor exercise capacity might cause sarcopenia and lower limb muscle weakness, which has been related to increased fall risk and, hence, increased risk of fracture. However, more research concerning the underlying pathophysiological mechanism of the relationship between low body mass and fat-free mass and osteoporosis is warranted in patients with COPD.

Fat mass

Overweight and obesity are, in addition to underweight, common in patients with COPD. Indeed, in a recent study 28–64% of male COPD patients and 33–50% of female COPD patients were overweight (BMI >25 kg·m⁻²) [39]. Notably, an overweight or obese BMI is protective against osteoporosis [44]. This might be due to an interaction between fat and bone tissue such as the effects of fat mass on the secretion of bone active hormones from the pancreatic β -cells (e.g. insulin and amylin) and the secretion of bone active hormones from adipocytes (e.g. leptin) [44].

Several studies have investigated the effects of leptin, an adipokine which is related to the amount of body fat [44, 45]. Leptin acts *via* the central nervous system and *via* the circulation, resulting in different effects on bone metabolism (fig. 2). Circulating leptin increases the proliferation and differentiation of osteoblasts and promotes bone nodule formation. It also regulates osteoclast development, at least partly, through the RANK/RANKL/OPG pathway, which results in net bone formation. Leptin has the opposite effect *via* the central nervous system, by influencing satiety and insulin secretion. It is believed that the local effects of leptin from adipose tissue are dominant over the central effects, resulting in a stronger skeleton, which is needed to support a greater soft tissue mass [44].

In patients with COPD, an overweight or obese BMI was shown to be protective against osteoporosis [22]. More recently, adipose tissue leptin and OPG expressions correlated positively with bone density variables and serum β -crosslap concentrations in 19 COPD patients with osteoporosis and 21 COPD patients with normal bone mass [46]. These findings might suggest that leptin and OPG act as mediators between fat mass and bone density in patients with COPD. However, more research on the interaction between fat and bone is warranted in patients with COPD.

Corticosteroids

Oral and inhaled corticosteroids are widely used in patients with COPD despite their adverse effects, such as oropharyngeal candidiasis, hoarseness and pneumonia [47]. In addition, the use of oral corticosteroids has been associated with decreased bone mass and increased risk of fracture. Indeed, the total cumulative dose of oral corticosteroids was inversely correlated with bone mineral density [48], and prior or current exposure to oral corticosteroids was associated with increased risk of fracture [49]. With respect to COPD patients, patients receiving oral corticosteroids were more likely to have one or more vertebral fractures [50, 51].

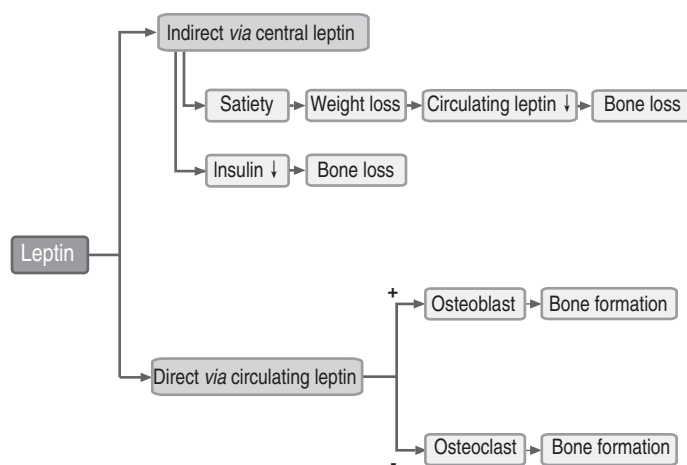


Figure 2. The effects of leptin on bone metabolism. +: stimulate; -: inhibit.

The effects of inhaled corticosteroids on bone health are less clear. A randomised controlled trial in 658 patients with moderate-to-severe COPD demonstrated that inhaled corticosteroids had no effect on bone mineral density at the hip and lumbar spine over 3 years [10]. However, a case–control study including 1,708 cases with non-vertebral fractures and 6,817 matched controls showed that the use of high-dose corticosteroids ($\geq 700\text{ }\mu\text{g}$ per day) was associated with increased risk of fracture compared with patients who did not use inhaled corticosteroids [52]. More recently, a systematic review concluded that long-term use of inhaled fluticasone or budesonide was associated with a dose-dependent increased risk of fracture [53]. Although accumulating evidence shows that the use of inhaled corticosteroids is correlated with increased risk of fracture, there is a need for more prospective studies that correct for confounders such as COPD severity.

Corticosteroids cause bone loss due to disruption of bone remodelling. Several mechanisms have been associated with corticosteroid-induced osteoporosis including impaired calcium intestinal absorption, decreased formation of osteoblasts, increased osteocytes apoptosis and altered sex hormone status in both males and females [9, 54]. In addition, corticosteroids might also cause muscle dysfunction resulting in increased risk of falls (table 2).

Since oral and inhaled corticosteroids have been correlated with increased risk of fracture, clinicians should carefully consider the risk of fracture associated with the use of oral and inhaled corticosteroids for treating and preventing exacerbations.

Vitamin D deficiency

Vitamin D deficiency is related to osteoporosis and is highly prevalent in patients with COPD. The prevalence of vitamin D deficiency, defined as plasma 25-hydroxyvitamin D concentrations $<50\text{ nmol}\cdot\text{L}^{-1}$, was 58% in a cross-sectional study with 151 COPD patients entering pulmonary rehabilitation during the summer [56]. The prevalence of vitamin D deficiency seems to be higher in patients with COPD than in subjects without coexisting COPD, and it seems to be related to the severity of COPD. In the Bergen COPD cohort study, the prevalence of vitamin D deficiency was higher in the COPD patients than in the control subjects independent of season, age, smoking, comorbidities and BMI [57]. In addition, the prevalence of vitamin D deficiency was 39% in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I, 47% in GOLD stage II, 60% in GOLD stage III and 77% in GOLD stage IV COPD patients [58]. There are several potential explanations for the increased risk of vitamin D deficiency in patients with COPD including poor diet, less exposure to sunlight due to poor physical activity, accelerated skin ageing due to smoking, renal dysfunction and treatment with corticosteroids.

Table 2. Metabolic effects of corticosteroids leading to bone loss
Effects on calcium metabolism Decrease in intestinal absorption of calcium and phosphate Increase in urinary calcium excretion Factors listed above promote the development of secondary hyperparathyroidism, which can increase bone resorption
Effects on sex hormones Direct and indirect effects on adrenal androgen and gonadal hormone release leading to the loss of anabolic effects of these hormones on bone formation and resorption
Direct bone effects Inhibition of osteoclast proliferation Inhibition of osteoclast attachment to bone matrix Inhibition of type I collagen and other proteins produced by osteoblasts
Other effects Steroid myopathy may slow or prevent exercise-induced benefits in bone formation as well as reduce normal physical forces of muscle tension on bone
Reproduced and modified from [55] with permission from the publisher.

The uptake of vitamin D and its role in bone homeostasis is well established. Humans receive vitamin D from exposure to sunlight, their diet (*e.g.* oily fish, butter and eggs) and from dietary supplements. In the liver, vitamin D₃ is metabolised to 25-hydroxyvitamin D, which is the major circulating metabolite of vitamin D. 25-hydroxyvitamin D is metabolised further to its active form, 1,25-dihydroxyvitamin D in the kidneys by the enzyme 1- α -hydroxylase. The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma PTH levels and serum calcium and phosphorus levels. The efficiency of intestinal calcium and phosphorus absorption is increased through the interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor. In case of vitamin D deficiency, decreased calcium absorption causes a compensatory increase in PTH. PTH enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25-dihydroxyvitamin D. PTH also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts. Osteoclasts dissolve the mineralised collagen matrix in bone, causing osteopenia and osteoporosis [59]. In addition, low 25-hydroxyvitamin D concentrations might also cause muscle dysfunction and thus increase the risk of falls, resulting in increased risk of fracture [60].

Although the role of vitamin D in bone health is well established in non-COPD populations, research in patients with COPD is limited. In underweight patients with end-stage pulmonary diseases waiting for lung transplantation, vitamin D deficiency was associated with reduced femur neck T-scores [61], and in COPD patients admitted for pulmonary rehabilitation vitamin D concentration was positively correlated with the lowest T-score of the hip and lumbar spine [56].

Physical inactivity

COPD patients are less physically active compared with control subjects [62]. In general, reduced physical activity is associated with bone loss and osteoporosis related fractures [63, 64], whereas exercise interventions may increase bone mineral density [65] and reduce the risk of falls and fractures [66]. In COPD patients, research on a relationship between physical activity and bone health is limited. SILVA *et al.* [19] showed that the International Physical Activity Questionnaire total activity score was related to the T-score of the femoral neck in 95 COPD patients, and NISHIMURA *et al.* [67] demonstrated that the 12-minute walk test was related to changes in bone mineral content in 22 COPD patients.

Smoking and alcohol use

Smoking is a risk factor for both osteoporosis [2] and COPD [29]. Smoking has been found to induce parenchymal destruction by inflammation. This parenchymal destruction occurs in an early stage of COPD and increases with more pack-years of smoking. In addition to parenchymal destruction, smoking has been associated with osteoporosis. Indeed, smokers had a 2–4-fold increased odds ratio for osteoporotic fractures compared with non smokers. The effect of smoking on bone loss has been suggested to be dose-dependent and related to several mechanisms [68]. First, smoking may increase bone loss through its effect on body weight. Smokers weigh less than non smokers and smoking cessation has been associated with increased weight within 3 months after cessation. Secondly, smoking might influence bone health through an earlier menopause because, on average, smoking females begin natural menopause 1–2 years earlier than non smokers, and age at menopause is a strong predictor of osteoporosis. Thirdly, cigarette smoke negatively affects hormones and enzymes engaged in the regulation of bone metabolism such as PTH and alkaline phosphatase.

COPD has been associated with high alcohol consumption in Japan [69] but not yet in the Caucasian population. Since alcohol consumption is recognised as a risk factor for osteoporosis [70, 71], it might be that increased alcohol consumption contributes to osteoporosis in patients with COPD. The mechanisms of the action of ethanol on bone are not completely understood, but these are suggested to be both indirect and direct. Indirectly, high alcohol consumption might interact with bone tissue *via* poor nutritional intake and caloric restriction, which results in a

reduced body and fat mass. In addition, alcohol consumption might also interact directly with bone remodelling by changes on the number and activity of osteoblasts and osteoclasts, increased osteocytes apoptosis, increased oxidative stress and increased fat accumulation in the bone marrow [71].

Taken together, both COPD and osteoporosis will particularly occur later in life and are dependent on common shared risk factors such as nutritional and lifestyle factors. However, more research is warranted to discover whether COPD in itself is an independent risk factor due to shared underlying mechanisms such as systemic inflammation and the use of corticosteroids.

Non-pharmacological and pharmacological treatment

Since several lifestyle factors, such as smoking, alcohol use and physical inactivity, have been associated with fractures due to osteoporosis, intervention against these factors might improve bone density and reduce risk of fracture. A systematic review stated that exercise had a positive effect on bone mass in post-menopausal females [65], and smoking cessation was associated with improvement in bone density [72]. Although multidisciplinary rehabilitation in patients with COPD has shown to have positive short-term and long-term functional effects, research on the effects of multidisciplinary rehabilitation on bone density and fracture risk is still lacking.

Calcium and vitamin D supplementation

Nowadays, calcium and vitamin D supplementation are recommended in the treatment of osteoporosis since they have positive effects on bone health and muscle function, resulting in reduced risk of fracture. A meta-analysis stated that calcium supplementation alone or in combination with vitamin D was effective in the preventive treatment of osteoporotic fracture [73]. In addition, another meta-analysis stated that vitamin D supplementation with doses of 700–800 IU per day reduced the relative risk of hip fracture by 26% and of any non-vertebral fracture by 23% compared with calcium supplementation or placebo in individuals aged 60 years or older [74]. In contrast, a Cochrane review stated that vitamin D without calcium supplementation appeared unlikely to be effective in preventing hip fracture, vertebral fracture or any new fracture [75]. These data suggest that both calcium and vitamin D are important in the prevention of osteoporotic fracture. In addition to its effect on fracture risk, vitamin D supplementation had beneficial effects on fall prevention among ambulatory or institutionalised older individuals with stable health [76]. Vitamin D supplementation with doses of 700–1,000 IU per day reduced falls by 19–26%, whereas vitamin D doses <700 IU did not prevent falls [77].

Based on evidence from randomised controlled trials and meta-analyses, it has been suggested that adequate vitamin D supplementation with doses of at least 700 IU per day is required for improving physical function, and prevention of falls and fractures in the elderly [78]. Additional calcium supplementation may be considered when dietary calcium intake is <700 mg per day, using a supplementation dose that leads to a maximum total daily calcium intake of 1,000–1,200 mg [79]. However, dietary advice to attain an adequate calcium intake is preferred to calcium supplementation, since calcium supplementation has been associated with increased risk of myocardial infarction [79].

Antiresorptive therapy

The role of bisphosphonates in the prevention and treatment of osteoporosis is well established. Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate and inhibit calcification by binding to hydroxyapatite crystals. In addition, bisphosphonates inhibit hydroxyapatite breakdown, thereby effectively suppressing bone resorption. It has been suggested that bisphosphonates also function to limit both osteoblast and osteocytes apoptosis. In post-menopausal females with osteoporosis, alendronate was associated with significant and clinically important reductions in the incidence of hip fracture [80]. In patients treated with corticosteroids, bisphosphonates were shown to increase bone mineral density and prevent the development of

new fractures [81]. In patients with airway disorders (asthma or chronic obstructive airway disease), daily intake of alendronate for 12 months was shown to significantly improve bone mineral density at the lumbar spine [82].

In addition to bisphosphonates, teriparatide and denosumab have been shown to be effective in reducing the risk of fragility fractures [83]. In patients with corticosteroid-induced osteoporosis, patients treated with teriparatide had an even greater increase in lumbar spine bone mineral density and fewer incidental vertebral fractures than patients treated daily with alendronate [84]. Denosumab, a human monoclonal antibody to RANKL, is a relatively new drug that prevents the interaction of RANKL with RANK, thereby blocking the formation, function and survival of osteoclasts and resulting in decreased bone resorption. In post-menopausal females with osteoporosis, denosumab was associated with a significant reduction in the risk of vertebral as well as hip and other non-vertebral fractures [85].

COPD-specific recommendations

Currently, osteoporosis is generally recognised as one of the systemic manifestations of COPD which contribute to worsening of the disease progression. Patients at risk of developing osteopenia or osteoporosis particularly include patients with advanced age, low body mass, frequent use of oral corticosteroids and vitamin D deficiency. These patients, but preferably all patients, should be screened for osteoporosis by DXA scan and vertebral fracture assessment, and, if necessary, treatment should be initiated. As no COPD-specific treatment has been developed yet, standard treatment for osteopenia and osteoporosis should be prescribed. However, COPD patients who use corticosteroids should be treated according to the guidelines for management of corticosteroid-induced osteoporosis [86]. The American College of Rheumatology recommends a daily calcium intake of 1,200–1,500 mg per day and vitamin D supplementation to achieve “therapeutic” vitamin D concentrations or vitamin D dosages of 800–1,000 units per day in all patients who use corticosteroids [87]. In addition, they recommend bisphosphonates in patients at low risk of fractures who use ≥ 7.5 mg prednisone equivalents per day, and in patients at medium or high risk of fractures who use any dose of corticosteroids.

Conclusion

Since osteoporosis is highly prevalent in patients with COPD and might contribute to the morbidity and mortality, chest physicians should screen all COPD patients at risk for osteoporosis. Diagnosis of osteoporosis should be based on bone mineral density assessed on DXA and vertebral fracture assessment on radiographs of the spine. The main risk factors of osteoporosis in COPD include advanced age, low body and muscle mass, smoking, alcohol use and vitamin D deficiency. In addition to these main risk factors, COPD-specific factors such as the use of corticosteroids and systemic inflammation might contribute to the development of osteoporosis in patients with COPD. Treatment of osteoporosis is primarily focused on reducing the risk of fracture and include intervention of risk factors by nutritional and lifestyle guidelines, calcium and vitamin D supplementation and antiresorptive therapy (e.g. bisphosphonates). In order to prevent and optimise treatment of osteoporosis in COPD, more research on its underlying pathophysiological mechanisms is warranted.

Statement of Interest

None declared.

References

1. Lehouck A, Boonen S, Decramer M, *et al.* COPD, bone metabolism, and osteoporosis. *Chest* 2011; 139: 648–657.
2. WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and Management of Osteoporosis: report of a WHO scientific group. WHO technical report series; 920. Geneva, World Health Organisation, 2003.

3. Lyles KW, Gold DT, Shipp KM, *et al.* Association of osteoporotic vertebral compression fractures with impaired functional status. *Am J Med* 1993; 94: 595–601.
4. Myers AH, Robinson EG, Van Natta ML, *et al.* Hip fractures among the elderly: factors associated with in-hospital mortality. *Am J Epidemiol* 1991; 134: 1128–1137.
5. Lewiecki EM, Gordon CM, Baim S, *et al.* International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions. *Bone* 2008; 43: 1115–1121.
6. Papaioannou A, Parkinson W, Ferko N, *et al.* Prevalence of vertebral fractures among patients with chronic obstructive pulmonary disease in Canada. *Osteoporos Int* 2003; 14: 913–917.
7. Lindsay R, Silverman SL, Cooper C, *et al.* Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; 285: 320–323.
8. Genant HK, Wu CY, van Kuijk C, *et al.* Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993; 8: 1137–1148.
9. Ferguson GT, Calverley PM, Anderson JA, *et al.* Prevalence and progression of osteoporosis in patients with COPD: results from the Towards a Revolution in COPD Health study. *Chest* 2009; 136: 1456–1465.
10. Hardy R, Cooper MS. Bone loss in inflammatory disorders. *J Endocrinol* 2009; 201: 309–320.
11. Graat-Verboom L, van den Borne BE, Smeenk FW, *et al.* Osteoporosis in COPD outpatients based on bone mineral density and vertebral fractures. *J Bone Miner Res* 2011; 26: 561–568.
12. Bolton CE, Ionescu AA, Shiels KM, *et al.* Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 1286–1293.
13. Sabit R, Bolton CE, Edwards PH, *et al.* Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 1259–1265.
14. Papaioannou A, Kennedy CC, Cranney A, *et al.* Risk factors for low BMD in healthy men age 50 years or older: a systematic review. *Osteoporos Int* 2009; 20: 507–518.
15. Waugh EJ, Lam MA, Hawker GA, *et al.* Risk factors for low bone mass in healthy 40–60 year old women: a systematic review of the literature. *Osteoporos Int* 2009; 20: 1–21.
16. Kanis JA, Johnell O, Oden A, *et al.* FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; 19: 385–397.
17. Sin DD, Man JP, Man SF. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am J Med* 2003; 114: 10–14.
18. Lekamwasam S, Trivedi DP, Khaw KT. An association between respiratory function and bone mineral density in women from the general community: a cross sectional study. *Osteoporos Int* 2002; 13: 710–715.
19. Silva DR, Coelho AC, Dumke A, *et al.* Osteoporosis prevalence and associated factors in patients with COPD: a cross-sectional study. *Respir Care* 2011; 56: 961–968.
20. Graat-Verboom L, Wouters EF, Smeenk FW, *et al.* Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J* 2009; 34: 209–218.
21. Coin A, Sergi G, Marin S, *et al.* Predictors of low bone mineral density in elderly males with chronic obstructive pulmonary disease: the role of body mass index. *Aging Male* 2010; 13: 142–147.
22. Graat-Verboom L, Spruit MA, van den Borne BE, *et al.* Correlates of osteoporosis in chronic obstructive pulmonary disease: an underestimated systemic component. *Respir Med* 2009; 103: 1143–1151.
23. Bon J. Does radiographic emphysema correlate with low bone mineral density? *Curr Opin Pulm Med* 2012; 18: 125–130.
24. Engelen MP, Schols AM, Lamers RJ, *et al.* Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. *Clin Nutr* 1999; 18: 275–280.
25. Bon J, Fuhrman CR, Weissfeld JL, *et al.* Radiographic emphysema predicts low bone mineral density in a tobacco-exposed cohort. *Am J Respir Crit Care Med* 2011; 183: 885–890.
26. Ohara T, Hirai T, Muro S, *et al.* Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. *Chest* 2008; 134: 1244–1249.
27. Bai P, Sun Y, Jin J, *et al.* Disturbance of the OPG/RANK/RANKL pathway and systemic inflammation in COPD patients with emphysema and osteoporosis. *Respir Res* 2011; 12: 157.
28. Kneidinger N, Yildirim AO, Callegari J, *et al.* Activation of the WNT/beta-catenin pathway attenuates experimental emphysema. *Am J Respir Crit Care Med* 2011; 183: 723–733.
29. Afonso AS, Verhamme KM, Sturkenboom MC, *et al.* COPD in the general population: prevalence, incidence and survival. *Respir Med* 2011; 105: 1872–1884.
30. Faner R, Rojas M, MacNee W, *et al.* Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012; 186: 306–313.
31. Nadeem A, Raj HG, Chhabra SK. Increased oxidative stress and altered levels of antioxidants in chronic obstructive pulmonary disease. *Inflammation* 2005; 29: 23–32.
32. Savale L, Chaouat A, Bastuji-Garin S, *et al.* Shortened telomeres in circulating leukocytes of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 179: 566–571.
33. Lee J, Sandford A, Man P, *et al.* Is the aging process accelerated in chronic obstructive pulmonary disease? *Curr Opin Pulm Med* 2011; 17: 90–97.
34. Syed FA, Ng AC. The pathophysiology of the aging skeleton. *Curr Osteoporos Rep* 2010; 8: 235–240.
35. Sturnieks DL, St George R, Lord SR. Balance disorders in the elderly. *Neurophysiol Clin* 2008; 38: 467–478.

36. Nguyen ND, Pongchaiyakul C, Center JR, *et al.* Identification of high-risk individuals for hip fracture: a 14-year prospective study. *J Bone Miner Res* 2005; 20: 1921–1928.
37. Schols AM, Mostert R, Soeters PB, *et al.* Body composition and exercise performance in patients with chronic obstructive pulmonary disease. *Thorax* 1991; 46: 695–699.
38. Mostert R, Goris A, Welting-Scheepers C, *et al.* Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 2000; 94: 859–867.
39. Vestbo J, Prescott E, Almdal T, *et al.* Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 2006; 173: 79–83.
40. Bolton CE, Cannings-John R, Edwards PH, *et al.* What community measurements can be used to predict bone disease in patients with COPD? *Respir Med* 2008; 102: 651–657.
41. Cavanagh PR, Licata AA, Rice AJ. Exercise and pharmacological countermeasures for bone loss during long-duration space flight. *Gravit Space Biol Bull* 2005; 18: 39–58.
42. LeBlanc AD, Schneider VS, Evans HJ, *et al.* Bone mineral loss and recovery after 17 weeks of bed rest. *J Bone Miner Res* 1990; 5: 843–850.
43. Takata S, Yasui N. Disuse osteoporosis. *J Med Invest* 2001; 48: 147–156.
44. Reid IR. Fat and bone. *Arch Biochem Biophys* 2010; 503: 20–27.
45. Kawai M, de Paula FJ, Rosen CJ. New insights into osteoporosis: the bone-fat connection. *J Intern Med* 2012; 272: 317–329.
46. Pobeha P, Ukropec J, Skyba P, *et al.* Relationship between osteoporosis and adipose tissue leptin and osteoprotegerin in patients with chronic obstructive pulmonary disease. *Bone* 2011; 48: 1008–1014.
47. Yang IA, Clarke MS, Sim EH, *et al.* Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 7: CD002991.
48. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002; 13: 777–787.
49. Kanis JA, Johansson H, Oden A, *et al.* A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2004; 19: 893–899.
50. McEvoy CE, Ensrud KE, Bender E, *et al.* Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 704–709.
51. Walsh LJ, Wong CA, Osborne J, *et al.* Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* 2001; 56: 279–284.
52. Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 855–859.
53. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax* 2011; 66: 699–708.
54. Lafage-Proust MH, Boudignon B, Thomas T. Glucocorticoid-induced osteoporosis: pathophysiological data and recent treatments. *Joint Bone Spine* 2003; 70: 109–118.
55. Goldstein MF, Fallon JJ, Harning R. Chronic glucocorticoid therapy-induced osteoporosis in patients with obstructive lung disease. *Chest* 1999; 116: 1733–1749.
56. Romme EA, Rutten EP, Smeenk FW, *et al.* Vitamin D status is associated with bone mineral density and functional exercise capacity in patients with chronic obstructive pulmonary disease. *Ann Med* 2012 [Epub ahead of print DOI: 10.3109/07853890.2012.671536].
57. Persson LJ, Aanerud M, Hiemstra PS, *et al.* Chronic obstructive pulmonary disease is associated with low levels of vitamin D. *PLoS One* 2012; 7: e38934.
58. Janssens W, Bouillon R, Claes B, *et al.* Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* 2010; 65: 215–220.
59. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357: 266–281.
60. Dirks-Naylor AJ, Lennon-Edwards S. The effects of vitamin D on skeletal muscle function and cellular signaling. *J Steroid Biochem Mol Biol* 2011; 125: 159–168.
61. Forli L, Halse J, Haug E, *et al.* Vitamin D deficiency, bone mineral density and weight in patients with advanced pulmonary disease. *J Intern Med* 2004; 256: 56–62.
62. Vorrink SN, Kort HS, Troosters T, *et al.* Level of daily physical activity in individuals with COPD compared with healthy controls. *Respir Res* 2011; 12: 33.
63. Marie PJ, Kassem M. Extrinsic mechanisms involved in age-related defective bone formation. *J Clin Endocrinol Metab* 2011; 96: 600–609.
64. Pluijm SM, Koes B, de Laet C, *et al.* A simple risk score for the assessment of absolute fracture risk in general practice based on two longitudinal studies. *J Bone Miner Res* 2009; 24: 768–774.
65. Howe TE, Shea B, Dawson LJ, *et al.* Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev* 2011; 7: CD000333.
66. de Kam D, Smulders E, Weerdesteyn V, *et al.* Exercise interventions to reduce fall-related fractures and their risk factors in individuals with low bone density: a systematic review of randomized controlled trials. *Osteoporos Int* 2009; 20: 2111–2125.

67. Nishimura Y, Nakata H, Tsutsumi M, *et al.* Relationship between changes of bone mineral content and twelve-minute walking distance in men with chronic obstructive pulmonary disease: a longitudinal study. *Intern Med* 1997; 36: 450–453.
68. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int* 2001; 68: 259–270.
69. Hirayama F, Lee AH, Binns CW, *et al.* Alcohol consumption in patients with chronic obstructive pulmonary disease in Japan. *Asia Pac J Public Health* 2008; 20: Suppl, 87–94.
70. Fini M, Salamanna F, Veronesi F, *et al.* Role of obesity, alcohol and smoking on bone health. *Front Biosci (Elite Ed)* 2012; 4: 2686–2706.
71. Maurel DB, Boisseau N, Benhamou CL, *et al.* Alcohol and bone: review of dose effects and mechanisms. *Osteoporos Int* 2012; 23: 1–16.
72. Yoon V, Maalouf NM, Sakhaee K. The effects of smoking on bone metabolism. *Osteoporos Int* 2012; 23: 2081–2092.
73. Tang BM, Eslick GD, Nowson C, *et al.* Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007; 370: 657–666.
74. Bischoff-Ferrari HA, Willett WC, Wong JB, *et al.* Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005; 293: 2257–2264.
75. Avenell A, Gillespie WJ, Gillespie LD, *et al.* Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2005; 3: CD000227.
76. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, *et al.* Effect of vitamin D on falls: a meta-analysis. *JAMA* 2004; 291: 1999–2006.
77. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, *et al.* Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 2009; 339: b3692.
78. van den Bergh JP, Bours SP, van Geel TA, *et al.* Optimal use of vitamin D when treating osteoporosis. *Curr Osteoporos Rep* 2011; 9: 36–42.
79. Reid IR, Bolland MJ, Sambrook PN, *et al.* Calcium supplementation: balancing the cardiovascular risks. *Maturitas* 2011; 69: 289–295.
80. Papapoulos SE, Quandt SA, Liberman UA, *et al.* Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. *Osteoporos Int* 2005; 16: 468–474.
81. Miller PD. Bisphosphonates for the prevention and treatment of corticosteroid-induced osteoporosis. *Osteoporos Int* 2001; 12: Suppl. 3, S3–S10.
82. Smith BJ, Laslett LL, Pile KD, *et al.* Randomized controlled trial of alendronate in airways disease and low bone mineral density. *Chron Respir Dis* 2004; 1: 131–137.
83. Murad MH, Drake MT, Mullan RJ, *et al.* Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab* 2012; 97: 1871–1880.
84. Saag KG, Shane E, Boonen S, *et al.* Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med* 2007; 357: 2028–2039.
85. Cummings SR, San MJ, McClung MR, *et al.* Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009; 361: 756–765.
86. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med* 2011; 365: 62–70.
87. Grossman JM, Gordon R, Ranganath VK, *et al.* American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)* 2010; 62: 1515–1526.

Chapter 8

Gastro-oesophageal reflux disease and COPD



Anant R.C. Patel and John R. Hurst

SUMMARY: Gastro-oesophageal reflux (GOR) and GOR disease (GORD) are common conditions that appear more prevalent in patients with COPD than control subjects. This chapter reviews the epidemiology and potential mechanisms of such associations, explores the impact of GORD on COPD and, in particular, on COPD exacerbations, and outlines the evidence that intervention for GORD may impact on COPD outcomes.

KEYWORDS: COPD, exacerbation, reflux

Centre for Respiratory Medicine,
UCL Medical School, London, UK.

Correspondence: J.R. Hurst,
Academic Unit of Respiratory
Medicine, UCL, Hampstead Campus,
London, NW3 2PF, UK.
Email: j.hurst@medsch.ucl.ac.uk

Eur Respir Monogr 2013; 59: 105–116.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011812
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

This chapter considers the relevance of gastro-oesophageal reflux (GOR) and GOR disease (GORD) in COPD, particularly with regard to its association with more frequent exacerbations. Epidemiological and observational evidence linking these two seemingly independent conditions has been mounting for several years. No strong evidence of a causal link between GOR and COPD exacerbations has yet been found, although there is evidence of microaspiration of refluxate in some other respiratory conditions. Much work remains to be done to fully understand the mechanisms and impact of GOR and its therapy in COPD patients. In this chapter, we will review the epidemiology, the pathophysiology and the potential mechanisms of interaction between these two common conditions.

Definitions, symptoms and pathophysiology of GOR and GORD

GOR can be defined as the retrograde movement of the stomach contents through the lower oesophageal sphincter (LOS) into the oesophagus or more proximally (fig. 1) [1]. According to the Montreal consensus definition, GORD is: “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications” [2].

The symptoms of GORD are heterogenous but most commonly include episodic retrosternal burning (heartburn) and regurgitation of refluxate into the mouth or pharynx. However, less typical symptoms, such as chest pain and upper abdominal dyspeptic (discomfort) and dysmotility (fullness, bloating), are also common and are included in the Montreal definition [2].

The LOS normally contracts under autonomic nervous system control to a higher pressure than that present in the stomach. Relaxation in the tone occurs in response to oesophageal peristalsis following swallowing. Transient LOS relaxations (TLOSRS) unrelated to swallowing are seen in healthy subjects, but in health, oesophageal peristalsis and swallowed saliva quickly return refluxate from the oesophagus to the stomach and neutralise oesophageal acid. Although TLOSRS are not more common in patients with GORD, they are associated with an increased number of acid reflux episodes [3].

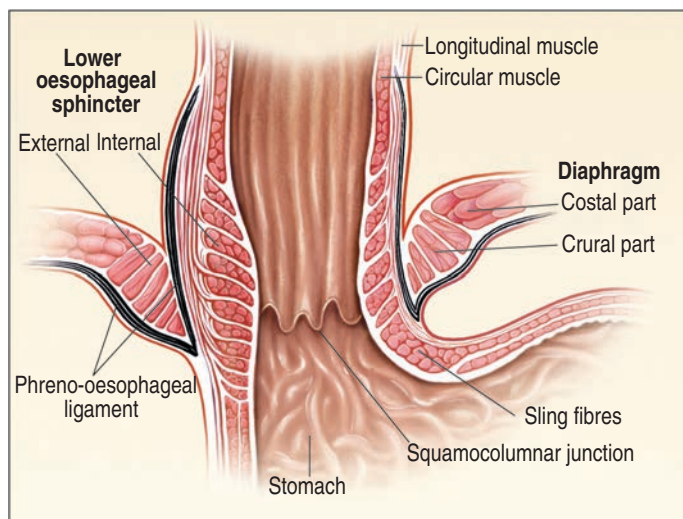


Figure 1. The lower oesophageal sphincter and the crural diaphragm constitute the intrinsic and extrinsic sphincters, respectively. The two sphincters are anatomically superimposed and are anchored to each other by the phreno-oesophageal ligament. Reproduced and modified from [1] with permission from the publisher.

symptoms, as extra-oesophageal symptoms are difficult to identify and quantify clinically or epidemiologically.

In erosive disease, the duration of exposure to the stomach contents correlates with the severity of mucosal injury. Mechanisms suggested in non-erosive disease include visceral hyper-sensitivity to acid [6], altered resistance of the mucosa to acid exposure or abnormal oesophageal contractions. This heterogeneity of response to GOR in the oesophagus may also be a feature in the airway.

It is important to note that non-acid reflux (containing bile salts, for example) may be important and, therefore, drugs suppressing acid secretion may not be universally effective for GORD. Bile acid concentrations in refluxate are known to be higher in nocturnal samples than those collected during the day [7]. The potential contents of refluxate are summarised in table 1.

Table 1. Refluxate constituents and their potential effect in COPD

Hydrochloric acid

Disrupts epithelial structure and increases cell shedding
Cyclo-oxygenase-2 inflammation is mediated by prostaglandin E2 and lipoxin A4 [8]
Stimulates adherence of *Streptococcus pneumoniae* to human tracheal epithelial cells *in vitro* via nuclear factor- κ B and increases interleukin-1 α and - β [9]

Pepsin

Increases permeability across the epithelium [10]
Upregulates intercellular adhesion molecule-1 [9]

Bile acids

More noxious at higher pH (*i.e.* those on acid suppression medication)
Pro-inflammatory on airway epithelial cells [11]
Induces transforming growth factor- β 1 and fibroblast proliferation [12]

Food/drink

Pancreatic enzymes

Laryngopharyngeal reflux is a common manifestation of GORD, which may present with throat symptoms alone and may therefore be of particular relevance in subjects with lung disease, given the increased upper respiratory tract symptoms [4]. GOR is a well-recognised cause of chronic cough that may contribute to COPD symptoms [5].

Some subjects develop endoscopy-proven oesophageal complications of GORD, such as oesophagitis, stricture, Barrett's oesophagus and adenocarcinoma, without prior classical symptoms of indigestion. This raises the possibility that extra-oesophageal complications of GOR may occur in COPD patients without typical symptoms. Most of the available data only relate to typical GORD

Epidemiology of GORD

GORD is a common condition, with 10–20% of adults in Western populations experiencing at least weekly symptoms [13] and 5% suffering from daily symptoms [14]. GORD is an episodic as well as relapsing and remitting, and often lifelong condition; many patients use long-term maintenance acid suppression (anti-secretory) therapies.

In COPD patients, regular GORD symptoms are around three times more prevalent than in the general

population at 30–60% [15] and, importantly, more prevalent than in smoking controls [16]. Moreover, significant symptoms are more common in COPD patients with more severe airflow limitation (fig. 2a). COPD patients are also more likely to be treated for GORD than controls (fig. 2b).

In a large UK primary care database, incident GORD was associated with a prior diagnosis of COPD [17]. In a 5-year longitudinal analysis of the same dataset, the relative risk (RR) of an incident GORD diagnosis among COPD patients was 1.46 (95% CI 1.19–1.78). However, the RR of an incident COPD diagnosis in patients with GORD was not significantly raised (1.17 (95% CI 0.91–1.49)) [18].

Potential mechanisms of interaction between GORD and COPD

There are a number of potential mechanisms through which GOR and GORD may be more common in COPD patients than controls. These are not yet well studied. However, associations between the two conditions appear robust and merit further research. The triggers of GOR are listed in table 2.

Symptoms of GORD are more common with increased intra-abdominal pressure, such as during coughing and straining, in those who are obese [19] and potentially in those with hyperinflated lungs where the diaphragm is displaced caudally [20].

Experimental acidification of the lower oesophagus increases cough responsiveness in patients with asthma [21] and chronic cough [22], perhaps mediated by a vago-vagal reflex. Airway hyperresponsiveness also increases in response to experimental oesophageal acidification, although no changes in spirometry have been observed [23].

Autonomic dysfunction is a feature of COPD [24], and neural control of LOS tone and gastric emptying may contribute to GOR in this population. Delayed gastric emptying is associated with refluxate that is less acidic but more proximal in the oesophagus, closer to the airway [25].

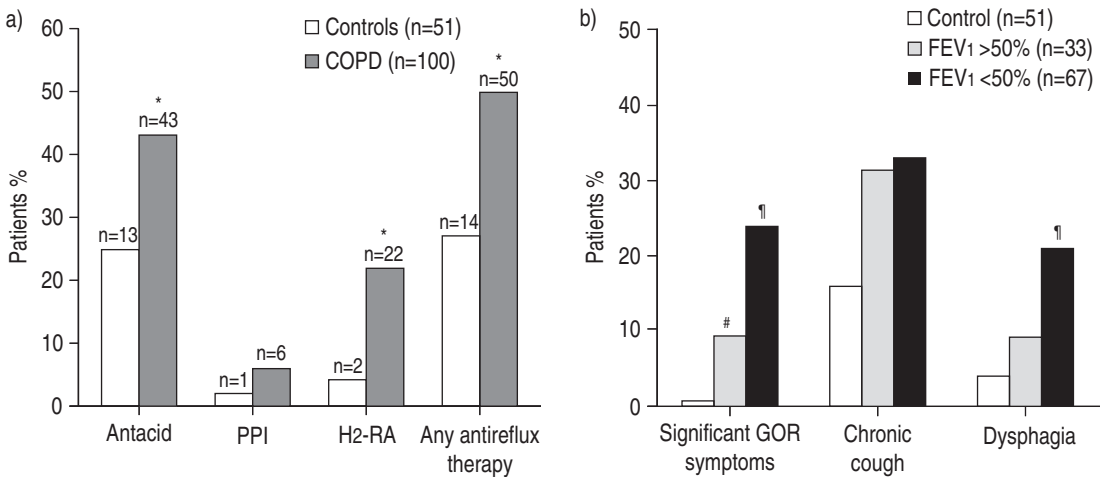


Figure 2. a) The proportion of COPD patients compared with control subjects receiving over-the-counter antacids (once or more per week), histamine 2 receptor antagonists (H2-RAs) daily or proton pump inhibitor (PPI) therapy daily. Some patients received multiple therapeutic regimens (*e.g.* antacids and other prescription-strength antireflux medications). *: $p < 0.05$, COPD patients *versus* control subjects. b) Patients with severe COPD, based on forced expiratory volume in 1 second (FEV₁) $\leq 50\%$ predicted, had a higher prevalence of significant gastro-oesophageal reflux (GOR) symptoms (heartburn and/or regurgitation once or more per week) compared with less severe COPD, based on FEV₁ $> 50\%$ pred, and control subjects. #: $p < 0.05$, FEV₁ $\leq 50\%$ pred *versus* control subjects. *: $p < 0.05$, FEV₁ $> 50\%$ pred *versus* control subjects; Reproduced and modified from [16] with permission from the publisher.

Table 2. Known triggers of gastro-oesophageal reflux

Increased intra-abdominal pressure

- Exercise
- Pregnancy
- Obesity
- Tight clothes

Compromised sphincter for anatomical reasons

- Hiatus hernia

Ingested substances

- Smoking
- Alcohol
- Caffeine
- Large meals

Gastric dysmotility

- Diabetic gastroparesis
- Drugs
 - Tricyclic antidepressants
 - Systemic anti-cholinergics
 - Nitrates
 - Calcium channel blockers

Refluxate need not always represent a liquid bolus; indeed, gaseous reflux is an important consideration, particularly in those with respiratory disease. It may be that gaseous reflux entails small volumes of aerosolised liquid refluxate, which may be easily aspirated by normal or laboured breathing.

Extra-oesophageal syndromes of GORD are well recognised and include reflux-mediated chronic cough, asthma, laryngitis and dental erosion (fig. 3) [2, 26].

Manometry studies have shown that episodes of reflux are more commonly detected in the lower oesophagus than in the upper third or pharynx; this may be an important consideration in those where microaspiration of refluxate may be suspected of contributing to respiratory symptoms (fig. 4) [27].

The pattern of regurgitation- and dysmotility-related GORD symptoms may be an important consideration in those with airway disease. COPD patients are more likely to have dysmotility symptoms, whereas asthma and control subjects experience more regurgitation [28].

The presence of a hiatus hernia is known to be important in perpetuating reflux (fig. 5) as the hernia can act as an acid pocket above the LOS. It is not currently known whether the presence of a hiatus hernia is more common in COPD patients than controls, although this has been demonstrated in patients with idiopathic pulmonary fibrosis (IPF) [29].

In 2004, the first study to explore 24-hour pH monitoring in COPD patients and controls was published (a previous study had been uncontrolled) [30]. 62% of the COPD patients had distal acid reflux compared with 19% of age-similar controls ($p=0.003$).

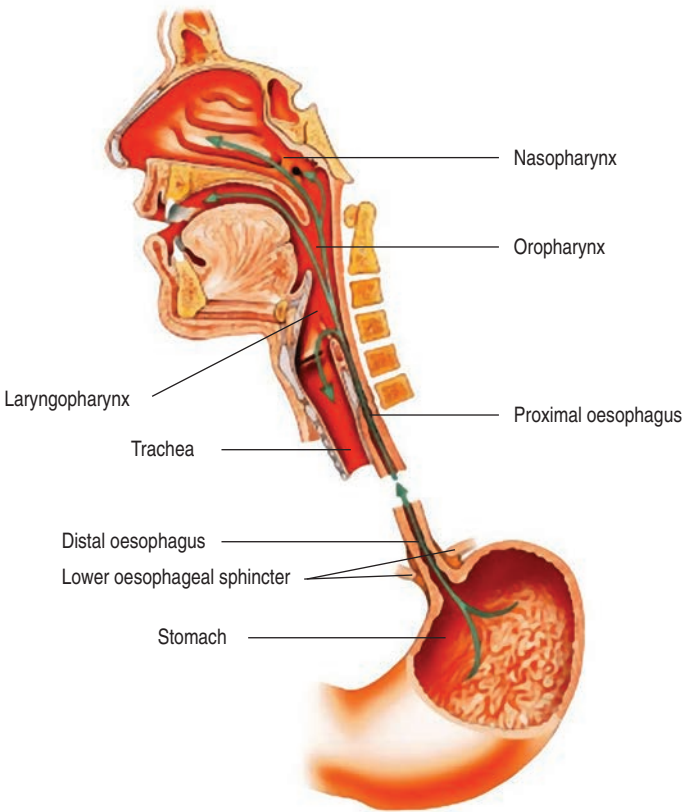


Figure 3. Anatomy of the head and neck. The arrow indicates the passage of gastro-oesophageal reflux proximally past the upper oesophageal sphincter. Laryngopharyngeal reflux results when refluxate reaches the vulnerable mucosa of the pharynx, larynx, oral cavity and nasal cavity. Reproduced and modified from [26] with permission from the publisher.

GORD symptoms were absent in 58% of the COPD patients, suggesting a high prevalence of asymptomatic acid reflux. In some patients, acidic GORD episodes were associated with oxygen desaturation, particularly when supine. A subsequent dual (distal and proximal) probe study found similar results and also noted abnormal proximal reflux [31]. Instillation of acid in the oesophagus of 12 COPD patients, most of whom had GORD, did not appear to provoke bronchoconstriction, in contrast to the response seen in asthmatics [32]. However, oesophageal acid clearance times were prolonged in COPD subjects, at least during the day.

Surgically induced GORD in rats causes microaspiration into the lungs with evidence of a marked inflammatory response in the bronchioles, with infiltration of lymphocytes, neutrophils and macrophages. It is of relevance to COPD that peribronchiolar lymphocytic infiltrates, thickened airway smooth muscle and goblet cell hyperplasia have also been noted [33].

From an evolutionary perspective, the upright bipedal stance of humans leads to loss of the right angle between the oesophagus and the hanging stomach seen in most other mammals, which may make reflux events more likely. Moreover, the anatomy of the human larynx to allow phonation provides less protection against microaspiration of regurgitated refluxate [34]. This may be compounded in COPD by disordered breathing and swallowing [35].

Salbutamol at high doses is known to reduce LOS tone and may increase reflux (fig. 6) [36]. Although systemic corticosteroids are a risk factor for peptic ulceration, there are no current data to suggest an association with GORD.

Lower lobe bronchiectasis in COPD is common and is associated with bacterial colonisation, greater airway inflammation and longer exacerbations [37]. Non-cystic fibrosis bronchiectasis has also been associated with GOR [38], although there are no currently available data to link the three conditions.

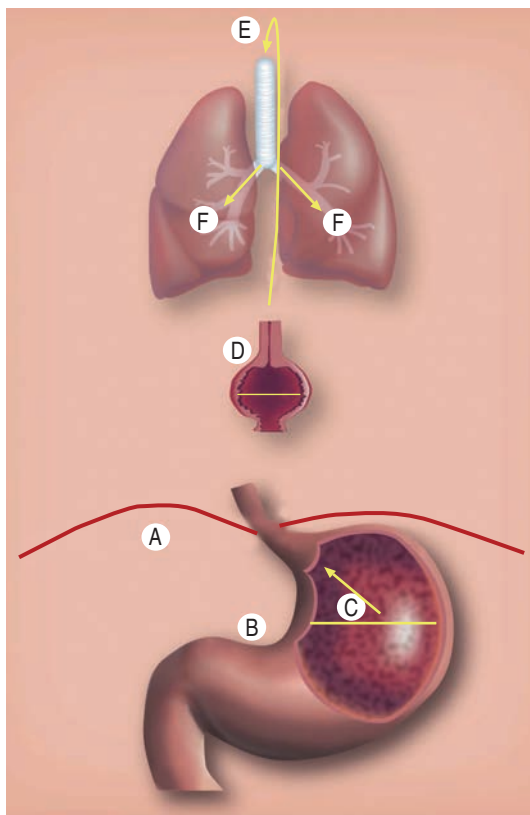


Figure 4. A proposed mechanism for microaspiration of gastric contents in COPD. A) The diaphragm displaced caudally from hyperinflated lungs exerts additional extrinsic pressure on the stomach. B) Increased use of abdominal muscles due to dyspnoea and coughing exerts extrinsic pressure on the stomach. C) The stomach contents pass retrograde through the lower oesophageal sphincter, which relaxes more often from changes in vagal tone in COPD and with COPD therapy. D) Increased intrathoracic pressure from hyperinflation and cardiac movements exerts extrinsic pressure on the oesophagus, facilitating retrograde movement of the refluxate (if present, hiatus hernia from a physically displaced diaphragm may act as a reservoir of refluxate in the thoracic cavity). E) Small quantities of liquid refluxate spill over into the airway. F) Constituents of aspirated refluxate enhance inflammation and increase susceptibility to exacerbation. Reproduced and modified from [27] with permission from the publisher.

Diagnosing GORD in COPD patients

The gold standard for diagnosing GORD is considered to be combined oesophageal pH impedance monitoring, as pH monitoring alone may fail to detect episodes of non-acid and weakly acid reflux [39]. Given the relative invasiveness of the test, investigation is generally reserved for patients with diagnostic doubt or a high symptom burden, or for research purposes.

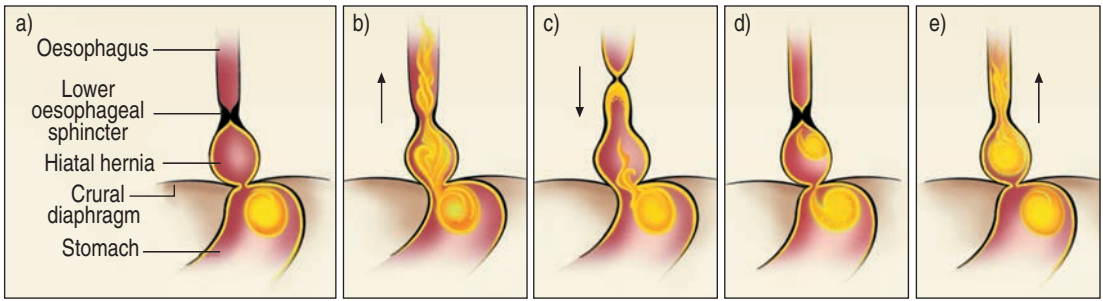


Figure 5. a) A hiatus hernia is an acquired herniation of part of the stomach through the diaphragm. b) After an episode of reflux, an oesophageal peristaltic contraction clears the bolus of acid from c) the oesophagus into d) the hiatus hernia. e) Subsequently, swallowing-induced relaxation of the lower oesophageal sphincter results in reflux of acid from the hernial sac into the oesophagus. This sequence can be repeated several times and results in markedly prolonged clearance of acid. Reproduced and modified from [1] with permission from the publisher.

Several symptom questionnaires have been validated for diagnosing GORD, and most scores respond to therapy [40]. They have the advantage of being noninvasive, cheap and easy to administer. However, complicating assessment, the relationships between symptoms, oesophageal mucosal appearances and findings in physiological studies are variable such that in a population survey of 1,000 subjects, two-thirds of those with symptoms had no oesophagitis and only one-third of those with visible oesophagitis reported symptoms [41].

The most common method of confirming the diagnosis in primary care is to make a clinical diagnosis based on symptoms and to follow this with an empirical trial of acid suppression therapy, most commonly with a proton pump inhibitor (PPI). Although this avoids invasive investigation, recent data have shown limited sensitivity and specificity of this approach [42]. The timing of PPI dosing is critical in treating GORD effectively. Usually taken only once daily, the medication should be taken 30–60 minutes before a meal as the drug irreversibly binds to and inhibits the proton pump only when it is activated, *i.e.* the drug has to be in the bloodstream at the

time of gastric distension [43, 44]. Proton pumps are turned over rapidly in parietal cells of the gastric mucosa; hence, daily dosing regimens of PPIs are more efficacious in terms of acid suppression than use on an as-required basis.

Endoscopy and laryngoscopy may be considered for the documentation of mucosal abnormalities when symptoms do not respond to therapy or are very severe, and this recommendation should not be different in COPD patients. Outside of this context, endoscopy does not have any significant clinical or research advantage in comparison with oesophageal manometry, and is therefore not standard practice. Patients with more severe COPD may not be fit for endoscopy, but a swallowed camera “pill” may provide an alternative.

In a study using scintigraphy, tracheobronchial aspiration of technetium-labelled orange juice has been shown to occur in patients with laryngeal symptoms of GORD, but not in

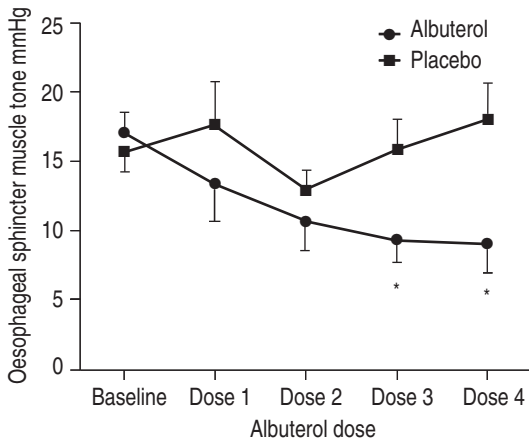


Figure 6. Salbutamol (albuterol) inhalation produces a dose-dependent reduction in lower oesophageal sphincter muscular tone. Reductions in tone were statistically significant ($p=0.02$) at cumulative dose 3 (7.5 mg total) and cumulative dose 4 (10.0 mg total). Error bars represent standard error of the mean. Reproduced and modified from [36] with permission from the publisher.

healthy controls [45]. Aerosolised acid in the pharynx can be identified and quantified using newer validated systems [46], although to date no published data exist for COPD.

Microaspiration of refluxate into the lower respiratory tract may be confirmed by the detection of gastric and duodenal substances that are not native to the lung. Pepsin and bile acids in airway samples may therefore be considered relevant biomarkers of reflux in COPD [44]. Pepsin was detectable in exhaled breath condensate (EBC) from COPD patients and correlated with symptoms on the Reflux Disease Questionnaire [47].

In routine clinical practice, the diagnosis of GORD should be commonly sought, given its high prevalence. In the absence of more COPD-specific data, the diagnosis of GORD should be confirmed in the same way it would be for the non-COPD population.

Associations between GORD and COPD exacerbations

The first suggestion of an association between COPD and GORD symptoms appeared in 2001 [16]. In a non-random comparison of 100 patients with COPD and 51 hospital-based controls without respiratory disease, the patients with COPD were more likely to experience weekly GORD symptoms (19% *versus* 0%, $p<0.001$) and it was suggested that these were more significant in patients with more severe COPD (23% *versus* 9%, $p=0.08$, based on a cut-off FEV₁ of 50% pred).

Exacerbations are of critical importance in COPD [48], as those who suffer more frequent exacerbations have more systemic and airway inflammation [49, 50], worse health status [51], accelerated decline in lung function [52] and increased mortality [53].

An association between GORD symptoms and exacerbations of COPD was first reported in 2006 [54]. In a small, selected group of 86 patients, self-reported exacerbation frequency was higher in patients with self-reported GORD (3.2 *versus* 1.6 per year, $p=0.02$). Results were confirmed in a 2007 study that quantified GORD using the Frequency Scale for Symptoms of Gastro-oesophageal Reflux Disease (FSSG) questionnaire [55]. The study demonstrated a significant association between FSSG score and exacerbation frequency ($r=0.24$, $p=0.03$), and an inverse relationship between FSSG score and exhaled breath pH, a marker of airway inflammation (although in this analysis a relationship between EBC pH and sputum inflammatory markers was not documented). The study did not demonstrate a difference in sputum inflammatory markers between COPD patients with and without GORD.

In the large ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study of over 2,000 participants, an analysis of comprehensive phenotyping data

Table 3. Factors associated with increased exacerbation frequency in a stepwise multivariate model

Parameter	Exacerbations			Overall model p-value
	≥2 <i>versus</i> 0	1 <i>versus</i> 0	≥2 <i>versus</i> 1	
Exacerbation during previous year	5.72 (4.47–7.31) ⁺	2.24 (1.77–2.84) ⁺	2.55 (1.96–3.31) ⁺	<0.001
FEV ₁ [#]	1.11 (1.08–1.14) ⁺	1.06 (1.03–1.08) ⁺	1.05 (1.02–1.09) ⁺	<0.001
SGRQ-C total score [†]	1.07 (1.04–1.10) ⁺	1.01 (0.99–1.04)	1.06 (1.03–1.09) ⁺	<0.001
History of reflux/heartburn	2.07 (1.58–2.72) ⁺	1.61 (1.23–2.10) ⁺	1.29 (0.97–1.70)	<0.001
WBC count 1 × 10 ⁹ cells·L ⁻¹ increase	1.08 (1.03–1.14) ⁺	1.02 (0.97–1.08)	1.06 (1.01–1.12) ⁺	0.007

Data are presented as odds ratio (95% confidence interval), unless otherwise stated. FEV₁: forced expiratory volume in 1 second; SGRQ-C: St George's Respiratory Questionnaire for COPD patients; WBC: white blood cell. [#]: 100-mL decrease; [†]: 4-point increase. ⁺: $p\leq 0.002$. Reproduced and modified from [56] with permission from the publisher.

confirmed that the presence of self-reported GORD increased the risk of exacerbation in a multivariate analysis: OR 2.07 (95% CI 1.58–2.72) for two or more *versus* no exacerbations ($p<0.001$). GORD was the only novel modifiable risk factor in the analysis (table 3) [56]. The prevalence of GORD was 27%, which underestimates the true prevalence. The concept that intervention for GOR may reduce exacerbations (see later) requires further testing but would be a novel way of reducing the burden of these important events.

Reciprocally, through increased symptom and/or changes in therapy, exacerbations themselves may increase the prevalence of GOR.

It has been suggested that an abnormal swallowing reflex is more common in patients with COPD than controls, and that in patients with COPD, those with an abnormal swallow reflex (assessed using a two-step swallowing provocation test) had a greater prevalence of GORD symptoms (6.75 *versus* 4.10 points on a self-reported questionnaire, $p=0.040$), a higher exacerbation frequency (2.8 *versus* 1.6 per year, $p=0.007$), more frequent isolation of sputum bacteria (45% *versus* 14%, $p=0.040$) and a higher systemic inflammatory response (C-reactive protein (CRP) 2.7 *versus* 1.0 $\text{mg}\cdot\text{L}^{-1}$, $p=0.040$) [35].

The presence of GORD in COPD outpatients was associated with lower quality of life scores using the 36-item Short-Form Health Survey (SF-36) in the 37% of patients who were identified as having GORD using the Mayo Clinic GOR questionnaire [57].

Does treating GORD affect outcomes in COPD?

Acid suppression therapies are effective at reducing or eliminating typical symptoms of GORD in most patients. However, a significant minority may continue to have symptoms related to non-acid or weakly acidic reflux, as gastric contents are still physically moving into the oesophagus.

The first randomised controlled trial of PPI for respiratory outcomes was performed in a mixed group of asthma and COPD patients with GORD who were taking inhaled steroids [58]. Those in the intervention arm of omeprazole 40 mg twice daily did not show any significant change in airway hyperresponsiveness or airflow limitation compared with those receiving placebo.

In a 12-month, randomised, single-blind trial of lansoprazole (15 mg once daily) in 100 patients with COPD, patients on active drug had a lower exacerbation frequency (0.34 *versus* 1.18 per year, $p<0.001$) and a lower risk of “catching frequent common colds” [59]. This study hypothesised on anti-inflammatory actions of the drug (see later) and patients with symptoms of GORD (but not necessarily asymptomatic reflux; this was not assessed) were excluded.

Intriguingly, PPI drugs may have an anti-inflammatory action, as reviewed in [60]. The drugs act primarily by blocking gastric acid secretion at parietal cell $\text{H}^+/\text{K}^+/\text{ATPase}$ pumps. As PPIs have an anti-inflammatory action, evidence of clinical benefit cannot be assumed to be due to effects on gastric acid secretion. The anti-inflammatory mechanism is unclear but may include free radical scavenging. In addition $\text{H}^+/\text{K}^+/\text{ATPase}$ pumps may be found intracellularly in the membranes of organelles, notably neutrophils phagolysosomes, where acidification is required for the oxidative burst, and expression of adhesion molecules involved in homing *via* modulation of intracellular calcium concentrations. Thus, there is reduced superoxide generation and chemotaxis with neutrophils pre-treated with omeprazole [61]. The mechanism remains unclear.

These effects are also seen in epithelial cells, including respiratory epithelial cells. Lansoprazole (and omeprazole) inhibits the expression of intracellular adhesion molecule (ICAM)-1 by cultured human tracheal epithelial cells [62], and decreases production of interleukin (IL)-6, IL-8 and tumour necrosis factor (TNF)- α , which are important cytokines in COPD. ICAM-1 is the receptor for major-group rhinovirus, the single most common infectious cause of exacerbation, and lansoprazole therefore inhibited rhinovirus infection in these cells. Once again, the precise mechanism of action is unclear.

Macrolide antibiotics, such as erythromycin and azithromycin, have been shown to reduce exacerbation frequency in COPD [63, 64]. Potential mechanisms for this include antibacterial and anti-inflammatory action, but macrolide drugs are also pro-kinetic in terms of gastric motility and it is possible that this mechanism may also be effective. Azithromycin at a dose of 250 mg per day has indeed been shown to reduce the number of reflux episodes, time of oesophageal acid exposure, and the size of hiatus hernias in patients with GORD [65].

Medications that act to prevent TLOSRs, such as γ -aminobutyric acid (GABA) β -agonists like baclofen, may be useful for those with persistent non-acid or weakly acidic reflux despite PPI therapy [66].

Nissen's fundoplication is a surgical procedure that is usually performed laparoscopically to prevent reflux through the LOS, and is an effective intervention for GORD [67]. There is currently no evidence base for this procedure in COPD patients with GORD.

The available therapies for GORD are summarised in table 4.

GORD and other primary respiratory diagnoses

GORD has been implicated in adversely affecting other respiratory conditions, in particular in IPF and lung transplant patients. The role of GORD in asthma appears less severe for the individual but potentially no less important at a population level where even small interactions between common diseases may be important.

Antireflux therapy in IPF is associated with prolonged survival [68], where there is known to be a very high prevalence of GOR -30–70% proximally, and 70–80% distally [69]. Fundoplication stabilises oxygen requirements in IPF but has no effect on FEV₁ [70].

In lung transplant recipients, the presence of bile acids in bronchoalveolar lavage fluid (BALF) is related to reduced survival [71], airway colonisation with *Pseudomonas aeruginosa* and airway inflammation (neutrophils and IL-8) [72]. GORD is strongly associated with bronchiolitis obliterans syndrome [73]. Bile acids were found in the BALF of 67% of clinically stable lung transplant recipients [74] and were associated with nocturnal weakly acidic reflux events.

In cystic fibrosis, there is a high prevalence of acid and bilious reflux [75], and bile acid concentration correlates with FEV₁ [76].

There is a high prevalence of GORD in asthmatics, which is associated with hospital admissions [77]. Large trials of PPI therapy have not proved successful in asthma [78], although when the doses are timed carefully 30–60 minutes before meals [46] and only those with GORD are targeted [79, 80], this approach may be more effective.

Conclusion

Symptoms of GORD are common in COPD patients and are associated with more frequent exacerbations in several datasets. The underlying mechanisms are poorly understood and have yet to be carefully studied. Several possible mechanisms exist, including microaspiration of gaseous and liquid refluxate into the lower respiratory tract, vago-vagal reflex from the oesophagus to the airway contributing to symptoms,

Table 4. Gastro-oesophageal reflux disease therapies

Anti-secretory

Proton pump inhibition
H2-RAs

Directly neutralising antacids

Prokinetic

Dopaminergic/5-HT
Macrolides

Antireflux

GABA
 β -agonists

Surgery

Laparoscopic Nissen's fundoplication

H2-RAs: histamine 2 receptor antagonists; 5-HT: 5-hydroxy-tryptamine; GABA: γ -aminobutyric acid.

and autonomic dysregulation of the LOS. The prevailing theory that GOR causes adverse effects in COPD is unproven; indeed, it is possible that exacerbations of COPD cause physiological disruption contributing to increased GOR. There remains the exciting possibility that treatment of GORD may lead to better outcomes in COPD. However, at present, there is a lack of the mechanistic studies needed to guide future randomised controlled trials of antireflux therapy. Clinically evident GORD should thus be asked about in COPD patients and managed as it would in the non-COPD population. We anticipate this field of research will mature in the coming years with the hope of tangible clinical benefits in large numbers of patients with COPD.

Statement of Interest

None declared.

References

1. Mittal RK, Balaban DH. The esophagogastric junction. *N Engl J Med* 1997; 336: 924–932.
2. Vakil N, van Zanten SV, Kahrilas P, *et al.* The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900–1920.
3. Iwakiri K, Hayashi Y, Kotoyori M, *et al.* Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of gastroesophageal reflux but are not the cause of reflux disease. *Dig Dis Sci* 2005; 50: 1072–1077.
4. Eryuksel E, Dogan M, Olgun S, *et al.* Incidence and treatment results of laryngopharyngeal reflux in chronic obstructive pulmonary disease. *Eur Arch Otorhinolaryngol* 2009; 266: 1267–1271.
5. Pauwels A, Blondeau K, Dupont L, *et al.* Cough and gastroesophageal reflux: from the gastroenterologist end. *Pulm Pharmacol Ther* 2009; 22: 135–138.
6. Trimble KC, Pryde A, Heading RC. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. *Gut* 1995; 37: 7–12.
7. Gotley DC, Morgan AP, Cooper MJ. Bile acid concentrations in the refluxate of patients with reflux oesophagitis. *Br J Surg* 1988; 75: 587–590.
8. Bonnans C, Fukunaga K, Levy MA, *et al.* Lipoxin A(4) regulates bronchial epithelial cell responses to acid injury. *Am J Pathol* 2006; 168: 1064–1072.
9. Ishizuka S, Yamaya M, Suzuki T, *et al.* Acid exposure stimulates the adherence of *Streptococcus pneumoniae* to cultured human airway epithelial cells: effects on platelet-activating factor receptor expression. *Am J Respir Cell Mol Biol* 2001; 24: 459–468.
10. Ohrui T, Yamaya M, Suzuki T, *et al.* Mechanisms of gastric juice-induced hyperpermeability of the cultured human tracheal epithelium. *Chest* 1997; 111: 454–459.
11. Mertens V, Blondeau K, Vanaudenaerde B, *et al.* Gastric juice from patients “on” acid suppressive therapy can still provoke a significant inflammatory reaction by human bronchial epithelial cells. *J Clin Gastroenterol* 2010; 44: e230–e235.
12. Perng DW, Chang KT, Su KC, *et al.* Exposure of airway epithelium to bile acids associated with gastroesophageal reflux symptoms: a relation to transforming growth factor- β 1 production and fibroblast proliferation. *Chest* 2007; 132: 1548–1556.
13. Dent J, El-Serag HB, Wallander MA, *et al.* Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; 54: 710–717.
14. Moayyedi P, Axon ATR. Review article: gastro-oesophageal reflux disease – the extent of the problem. *Aliment Pharmacol Ther* 2005; 22: 11–19.
15. Barr RG, Celli BR, Mannino DM, *et al.* Comorbidities, patient knowledge, and disease management in a national sample of patients with COPD. *Am J Med* 2009; 122: 348–355.
16. Mokhlesi B, Morris AL, Huang CF, *et al.* Increased prevalence of gastroesophageal reflux symptoms in patients with COPD. *Chest* 2001; 119: 1043–1048.
17. El-Serag H, Hill C, Jones R. Systematic review: the epidemiology of gastro-oesophageal reflux disease in primary care, using the UK General Practice Research Database. *Aliment Pharmacol Ther* 2009; 29: 470–480.
18. García-Rodríguez LA, Ruigómez A, Martín-Merino E, *et al.* Relationship between gastroesophageal reflux disease and COPD in UK primary care. *Chest* 2008; 134: 1223–1230.
19. Blondeau K, Boecxstaens V, Van Oudenhove L, *et al.* Increasing body weight enhances prevalence and proximal extent of reflux in GERD patients “on” and “off” PPI therapy. *Neurogastroenterol Motil* 2011; 23: 724–e327.
20. Liang BM, Feng YL. Association of gastroesophageal reflux disease symptoms with stable chronic obstructive pulmonary disease. *Lung* 2012; 190: 277–282.
21. Wu DN, Yamauchi K, Kobayashi H, *et al.* Effects of esophageal acid perfusion on cough responsiveness in patients with bronchial asthma. *Chest* 2002; 122: 505–509.
22. Javorkova N, Varechova S, Pecova R, *et al.* Acidification of the oesophagus acutely increases the cough sensitivity in patients with gastro-oesophageal reflux and chronic cough. *Neurogastroenterol Motil* 2008; 20: 119–124.

23. Wu DN, Tanifuji Y, Kobayashi H, *et al.* Effects of esophageal acid perfusion on airway hyperresponsiveness in patients with bronchial asthma. *Chest* 2000; 118: 1553–1556.
24. van Gestel A Jr, Steier J. Autonomic dysfunction in patients with chronic obstructive pulmonary disease. *J Thorac Dis* 2010; 2: 215–222.
25. Emerenziani S, Sifrim D. Gastroesophageal reflux and gastric emptying, revisited. *Curr Gastroenterol Rep* 2005; 7: 190–195.
26. Lipan MJ, Reidenberg JS, Laitman JT. Anatomy of reflux: A growing health problem affecting structures of the head and neck. *Anat Rec B New Anat* 2006; 289: 261–270.
27. Patel ARC, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. *Expert Rev Respir Med* 2011; 5: 647–662.
28. Shimizu Y, Dobashi K, Kusano M, *et al.* Different gastroesophageal reflux symptoms of middle-aged to elderly asthma and chronic obstructive pulmonary disease (COPD) patients. *J Clin Biochem Nutrition* 2012; 50: 169–175.
29. Noth I, Zangan SM, Soares RV, *et al.* Prevalence of hiatal hernia by blinded multidetector CT in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2012; 39: 344–351.
30. Casanova C, Baudet JS, del Valle Velasco M, *et al.* Increased gastro-oesophageal reflux disease in patients with severe COPD. *Eur Respir J* 2004; 23: 841–845.
31. Kempainen RR, Savik K, Whelan TP, *et al.* High prevalence of proximal and distal gastroesophageal reflux disease in advanced COPD. *Chest* 2007; 131: 1666–1671.
32. Orr WC, Shamma-Othman Z, Allen M, *et al.* Esophageal function and gastroesophageal reflux during sleep and waking in patients with chronic obstructive pulmonary disease. *Chest* 1992; 101: 1521–1525.
33. Oue K, Mukaisho KI, Higo T, *et al.* Histological examination of the relationship between respiratory disorders and repetitive microaspiration using a rat gastro-duodenal contents reflux model. *Exp Anim* 2011; 60: 141–150.
34. Laitman JT, Reidenberg JS. The human aerodigestive tract and gastroesophageal reflux: an evolutionary perspective. *Am J Med* 1997; 103: 2S–8S.
35. Terada K, Muro S, Ohara T, *et al.* Abnormal swallowing reflex and COPD exacerbations. *Chest* 2010; 137: 326–332.
36. Crowell MD, Zayat EN, Lacy BE, *et al.* The effects of an inhaled β_2 -adrenergic agonist on lower esophageal function: a dose-response study. *Chest* 2001; 120: 1184–1189.
37. Patel IS, Vlahos I, Wilkinson TMA, *et al.* Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400–407.
38. Lee AL, Button BM, Denehy L, *et al.* Gastro-oesophageal reflux in noncystic fibrosis bronchiectasis. *Pulm Med* 2011; 2011: 395020.
39. Aanen MC, Bredenoord AJ, Samsom M, *et al.* Reliability of oesophageal pH recording for the detection of gastro-oesophageal reflux. *Scand J Gastroenterol* 2008; 43: 1442–1447.
40. Modlin IM, Moss SF. Symptom evaluation in gastroesophageal reflux disease. *J Clin Gastroenterol* 2008; 42: 558–563.
41. Ronkainen J, Aro P, Storskrubb T, *et al.* Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005; 129: 1825–1831.
42. Bytzer P, Jones R, Vakil N, *et al.* Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2012; 10: 1360–1366.
43. Hatlebakk JG, Katz PO, Camacho-Lobato L, *et al.* Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. *Aliment Pharmacol Ther* 2000; 14: 1267–1272.
44. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 2000; 118: S9–S31.
45. Bestetti A, Carola F, Carnevali-Ricci P, *et al.* ^{99m}Tc -sulfur colloid gastroesophageal scintigraphy with late lung imaging to evaluate patients with posterior laryngitis. *J Nucl Med* 2000; 41: 1597–1602.
46. Pacheco-Galván A, Hart SP, Morice AH. Relationship between gastro-oesophageal reflux and airway diseases: the airway reflux paradigm. *Arch Bronconeumol* 2011; 47: 195–203.
47. Timms C, Thomas PS, Yates DH. Detection of gastro-oesophageal reflux disease (GORD) in patients with obstructive lung disease using exhaled breath profiling. *J Breath Res* 2012; 6: 016003.
48. Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370: 786–796.
49. Hurst JR, Donaldson GC, Perera WR, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 174: 867–874.
50. Bhowmik A, Seemungal TA, Sapsford RJ, *et al.* Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000; 55: 114–120.
51. Seemungal TA, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
52. Donaldson GC, Seemungal TAR, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
53. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931.
54. Rascon-Aguilar IE, Pamer M, Wludyka P, *et al.* Role of gastroesophageal reflux symptoms in exacerbations of COPD. *Chest* 2006; 130: 1096–1101.

55. Terada K, Muro S, Sato S, *et al.* Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. *Thorax* 2008; 63: 951–955.
56. Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.
57. Rascon-Aguilar IE, Pamer M, Wludyka P, *et al.* Poorly treated or unrecognized GERD reduces quality of life in patients with COPD. *Dig Dis Sci* 2011; 56: 1976–1980.
58. Boeree MJ, Peters FT, Postma DS, *et al.* No effects of high-dose omeprazole in patients with severe airway hyperresponsiveness and (a)symptomatic gastro-oesophageal reflux. *Eur Respir J* 1998; 11: 1070–1074.
59. Sasaki T, Nakayama K, Yasuda H, *et al.* A randomized, single-blind study of lansoprazole for the prevention of exacerbations of chronic obstructive pulmonary disease in older patients. *J Am Geriatr Soc* 2009; 57: 1453–1457.
60. Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig Dis Sci* 2009; 54: 2312–2317.
61. Wandall JH. Effects of omeprazole on neutrophil chemotaxis, super oxide production, degranulation, and translocation of cytochrome b-245. *Gut* 1992; 33: 617–621.
62. Sasaki T, Yamaya M, Yasuda H, *et al.* The proton pump inhibitor lansoprazole inhibits rhinovirus infection in cultured human tracheal epithelial cells. *Eur J Pharmacol* 2005; 509: 201–210.
63. Seemungal TAR, Wilkinson TMA, Hurst JR, *et al.* Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008; 178: 1139–1147.
64. Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689–698.
65. Rohof WO, Bennisink RJ, de Ruigh AA, *et al.* Effect of azithromycin on acid reflux, hiatus hernia and proximal acid pocket in the postprandial period. *Gut* 2012; 61: 1670–1677.
66. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut* 2012; 61: 1340–1354.
67. Niebisch S, Peters JH. Update on fundoplication for the treatment of GERD. *Curr Gastroenterol Rep* 2012; 14: 189–196.
68. Lee JS, Ryu JH, Elicker BM, *et al.* Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 1390–1394.
69. Lee JS, Collard HR, Raghu G, *et al.* Does chronic microaspiration cause idiopathic pulmonary fibrosis? *Am J Med* 2010; 123: 304–311.
70. Linden PA, Gilbert RJ, Yeap BY, *et al.* Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation. *J Thorac Cardiovasc Surg* 2006; 131: 438–446.
71. Mertens V, Blondeau K, Van Oudenhove L, *et al.* Bile acids aspiration reduces survival in lung transplant recipients with BOS despite azithromycin. *Am J Transplant* 2011; 11: 329–335.
72. Vos R, Blondeau K, Vanaudenaerde BM, *et al.* Airway colonization and gastric aspiration after lung transplantation: do birds of a feather flock together? *J Heart Lung Transplant* 2008; 27: 843–849.
73. Bobadilla JL, Jankowska-Gan E, Xu Q, *et al.* Reflux-induced collagen type V sensitization: potential mediator of bronchiolitis obliterans syndrome. *Chest* 2010; 138: 363–370.
74. Blondeau K, Mertens V, Vanaudenaerde BA, *et al.* Nocturnal weakly acidic reflux promotes aspiration of bile acids in lung transplant recipients. *J Heart Lung Transplant* 2009; 28: 141–148.
75. Aseeri A, Brodlie M, Lordan J, *et al.* Bile acids are present in the lower airways of people with cystic fibrosis. *Am J Respir Crit Care Med* 2012; 185: 463.
76. Blondeau K, Pauwels A, Dupont L, *et al.* Characteristics of gastroesophageal reflux and potential risk of gastric content aspiration in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2010; 50: 161–166.
77. Dal Negro RW, Turco P, Micheletto C, *et al.* Cost analysis of GER-induced asthma: a controlled study vs. atopic asthma of comparable severity. *Respir Med* 2007; 101: 1814–1820.
78. Mastrorade JG, Anthonisen NR, Castro M, *et al.* Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med* 2009; 360: 1487–1499.
79. Harding SM. Gastroesophageal reflux as an asthma trigger: acid stress. *Chest* 2004; 126: 1398–1399.
80. Bucknall C, Stanton A, Miller G, *et al.* The impact of normalization of esophageal acid profile by incremental proton pump inhibitors dosing in difficult asthma patients with proven gastro-esophageal acid reflux. *J Asthma* 2009; 46: 506–511.

Chapter 9

Metabolic syndrome and diabetes mellitus in COPD



Claire E. Wells and Emma H. Baker

SUMMARY: Metabolic syndrome is a complex set of inter-linked metabolic abnormalities, strongly associated with premature death from cardiovascular disease. Metabolic syndrome increases the risk of type 2 diabetes mellitus, with insulin resistance being central to the pathophysiology of both conditions.

People with COPD have multiple risk factors predisposing to metabolic syndrome and diabetes. They have an increased risk of obesity, tend to be sedentary, have increased inflammation and oxidative stress and are treated with corticosteroids. Diabetes mellitus and metabolic syndrome are around 1.5-times more common in people with COPD than in the general population.

Identification and treatment of metabolic syndrome and diabetes mellitus is important in all populations to reduce the lifetime risk of cardiovascular disease. However, in COPD patients, treatment of diabetes may also reduce pulmonary infection and exacerbations. Reversal of insulin resistance may reduce inflammation and skeletal muscle decline. Treatment strategies include exercise, dietary modification, weight loss and insulin-sensitising and lipid-lowering drugs.

KEYWORDS: Atherogenesis, inflammation, insulin resistance, lifestyle, obesity

Clinical Pharmacology, Division of Biomedical Sciences, St George's, University of London, London, UK.

Correspondence: E.H. Baker, Mailpoint J1A, 1st Floor Jenner Wing, Division of Biomedical Sciences, St George's, University of London, Cranmer Terrace, London, SW17 0RE, UK.
Email: ebaker@sgul.ac.uk

Eur Respir Monogr 2013; 59: 117–134.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10011912
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Metabolic syndrome and type 2 diabetes mellitus occur in people with obesity and insulin resistance and predispose to cardiovascular disease. They are strongly associated with COPD through common risk factors, as well as through consequences of, and treatments for, COPD. Both COPD and metabolic syndrome/diabetes are pro-inflammatory, and systemic inflammation is potentiated where they coexist. This may contribute to the reduced survival and increased frequency and duration of exacerbations in COPD patients with metabolic syndrome/diabetes. This chapter aims to raise awareness of the pathogenesis and consequences of metabolic syndrome/diabetes in COPD patients to improve management and reduce impact of these comorbidities.

Metabolic syndrome

Definition

Metabolic syndrome is a complex clustering of risk factors associated with development of atherosclerotic cardiovascular disease and type 2 diabetes. These risk factors are central obesity, elevated blood glucose, hypertension and dyslipidaemia (elevated triglycerides and low high-density lipoprotein (HDL) cholesterol). There are many different definitions of metabolic syndrome, which complicate interpretation of the literature. In 2009, a consensus meeting of diverse international societies issued a global statement, unifying the definition of metabolic syndrome as possession of any three of the following risk factors [1]: increased waist circumference (UK males >102 cm, females >88 cm); increased triglycerides (≥ 1.7 mmol·L⁻¹, or on treatment); reduced HDL cholesterol (≤ 1.0 mmol·L⁻¹ in men, ≤ 1.3 mmol·L⁻¹ in women, or on treatment); increased blood pressure (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg, or on treatment); raised fasting glucose (>5.5 mmol·L⁻¹, or on treatment).

Pathophysiology

Increased visceral adipose tissue is central to the development of metabolic syndrome. Visceral adipose tissue releases bioactive substances, including free fatty acids and adipocytokines into the circulation. Free fatty acids induce insulin resistance in liver and skeletal muscle, through intracellular fat deposition and alteration of signalling pathways, causing hyperglycaemia and dyslipidaemia [2]. Reactive insulin hypersecretion stimulates renal sodium reabsorption and sympathetic nervous system activity, driving hypertension [3]. Adipocytokines include hormones involved in the regulation of glucose and energy balance, such as leptin, adiponectin and resistin, and pro-inflammatory chemokines (e.g. monocyte chemotactic protein (MCP)-1, interleukin (IL)-8) and cytokines (e.g. tumour necrosis factor (TNF)- α , IL-6, IL-1) [4]. In visceral obesity, reduced secretion of adiponectin and increased secretion of resistin worsen insulin resistance, with loss of the beneficial anti-inflammatory and anti-atherogenic effects of adiponectin. Pro-inflammatory cytokines disrupt insulin receptor signalling, both directly [5] and through the activation of serine kinases [6], further worsening insulin resistance. Increased production of plasminogen activator inhibitor-1 and derangement of other coagulation factors leads to a prothrombotic state [7]. Oxidative stress is increased by the activation of biochemical pathways, with increased delivery of reactive oxygen species, decreased antioxidant protection and increased lipid peroxidation [8].

Not all people with abdominal obesity have metabolic syndrome and not all people with metabolic syndrome are obese. Other factors, which increase the risk of metabolic syndrome, include: genetics [9]; physical inactivity [10]; medications, including antiretroviral [11] and antipsychotic [12] drugs and older generation beta blockers [13]; and corticosteroid excess [14]. Activation of other pathways, including the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, and the renin–angiotensin–aldosterone system may also play a role [15].

Implications

People with metabolic syndrome are 1.5–3-times more likely to have cardiovascular disease [16, 17] and to experience a cardiovascular event [18, 19] than those without metabolic syndrome. All components of the metabolic syndrome cause endothelial dysfunction, which impairs nitric oxide mediated vasodilatation, promotes platelet adhesion and thrombosis, and impairs fibrinolysis [20]. Dyslipidaemia increases lipid infiltration into vessel walls and activates macrophages involved in the generation of atheromatous plaques [21]. Systemic inflammation and hypercoagulability augment atherogenesis and promote plaque instability, increasing the risk of cardiovascular events, such as myocardial infarction and stroke. Despite the strong association, a diagnosis of metabolic syndrome does not predict cardiovascular disease more effectively than the sum of its individual components [18] or the Framingham risk score [19].

Beyond cardiovascular disease, the metabolic syndrome and insulin resistance have been associated with reduced skeletal muscle mass and strength [22], and an increased risk of osteoporosis [23], cancer [24], depression [25] and cognitive impairment [26, 27].

Diabetes mellitus

Definition

The World Health Organization (WHO) defines diabetes as elevation of blood glucose (hyperglycaemia) to a level that increases the risk of microvascular damage [28]. Pre-diabetes is elevation of blood glucose above the normal range, but below that of clinical diabetes and includes the diagnoses of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)[28].

Pathophysiology

Type 2 diabetes is a condition characterised by insulin resistance and relative insulin deficiency, resulting in hyperglycaemia. The mechanisms underlying development of insulin resistance are those discussed for metabolic syndrome and people with metabolic syndrome have a five-fold increased risk of developing diabetes [29]. The initial pancreatic response to insulin resistance is insulin hypersecretion, with hyperinsulinaemia, contributing to endothelial dysfunction and vascular damage [30]. Subsequent pancreatic failure, in part mediated by lipotoxic effects of free fatty acids on pancreatic β cells, leads to relative insulin deficiency and hyperglycaemia [31].

Implications

Pre-diabetes is associated with a minor increase in the risk of microvascular and macrovascular disease [32]. Its main implications are through clustering with other components of the metabolic syndrome and in the likely progression to type 2 diabetes [33].

People with diabetes have a reduced life expectancy and diminished quality of life [28]. Much of this increased morbidity and mortality is attributable to microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease) [28].

Diabetes is also associated with an increased susceptibility to sepsis and infection [34]. Hyperglycaemia disrupts the host response to infection by impairing neutrophil function and humoral immunity [34]. Elevated glucose levels in tissues and secretions increase growth [35] and pathogenicity of infecting bacteria [36]. Hyperglycaemia drives inflammation and increases circulating pro-inflammatory cytokine concentrations [37].

Metabolic syndrome and diabetes in COPD

Prevalence

Metabolic syndrome and type 2 diabetes are common in COPD (tables 1 and 2). Metabolic syndrome affects 21–53% of people with COPD and, in cross-sectional studies, appears to be more prevalent in earlier stage COPD [39, 42]. Diabetes affects 2–37% of people with COPD, depending on the patient subgroup studied. Both conditions occur more often in people with COPD than in the general population. Metabolic syndrome is 1.3–1.5-times more common in COPD patients than in people with normal lung function (table 1). In population studies, COPD is consistently associated with a 1.4–2.0-fold increased risk of diabetes (table 2) [56–58, 61].

Table 1. Prevalence of metabolic syndrome (MetS) in people with COPD

Country [ref.]	Study and patients	Prevalence of MetS in COPD	Association of COPD with MetS
Korea [38]	133 people with newly-diagnosed COPD 1082 population controls	Males 33% Females 49% 21%	MetS less common in controls Males, no COPD 22% Females, no COPD 30% MetS more prevalent in earlier stages of COPD
Greece [39]	114 male COPD patients without significant comorbidities		
Turkey [40]	106 COPD patients with exacerbations seen at or admitted to hospital	27%	
Canada [41]	38 COPD patients; 34 control participants matched for age and sex	47%	21%
Germany [42]	30 patients with chronic bronchitis but normal lung function; 170 patients with COPD	GOLD stage I 50%, GOLD stage II 53%, GOLD stage III 37%, GOLD stage IV 44%	Chronic bronchitis 53%
France [43]	16 overweight COPD patients, 12 normal weight COPD patients	50%; 0%	Overweight/obese patients had higher TNF- α , IL-6, leptin and lower adiponectin
Japan [44]	7189 males aged 45–88 years at medical check-up, 9% had airflow obstruction		OR (95% CI) for MetS in people with GOLD II–IV COPD was 1.33 (1.01–1.76) compared to those with normal lung function
China [45]	Population-based survey of 7358 adults ≥ 50 years, 6.7% airflow obstruction		OR (95% CI) for MetS in those with airflow obstruction was 1.47 (1.12–1.92) compared to those without

GOLD: Global Initiative for Chronic Obstructive Lung Disease; TNF: tumour necrosis factor; IL: interleukin.

Mechanisms

The mechanisms underlying the increased prevalence of metabolic syndrome and diabetes in COPD include increased obesity, reduced physical activity, increased cigarette smoke and corticosteroid exposure and disease-related inflammation, oxidative stress and hypoxia.

Obesity

Obesity, defined as a body mass index (BMI) ≥ 30 kg·m⁻², is common in COPD, especially in people with less severe lung disease. In a Dutch primary care study, 18% of 317 COPD patients were obese [62], compared with 10–12% of the general population [63]. Obesity was more common in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I (16%) and II (24%) COPD than in GOLD stage IV disease (6%). In an American study, 54% of 355 people with COPD were obese [64] compared with 36% of the general population [65]. 61% COPD patients attending cardiopulmonary rehabilitation had central obesity measured by waist circumference compared with 32% matched controls [41]. Waist circumference was greater in mild-to-moderate COPD patients than in those with severe and very severe disease [42]. In COPD patients, increasing BMI was associated with increased adipose [66] and systemic [43] inflammation and reduced insulin sensitivity [66].

Physical activity

COPD patients have significantly reduced daily physical activity compared with healthy controls. In a review of 11 activity monitoring studies, COPD patients were active for 57% of the time of

Table 2. Prevalence of diabetes in people with COPD

Country [ref.]	Study and patients	Prevalence of diabetes	Association of COPD with diabetes
China [46]	495 people hospitalised for COPD exacerbations	11%	
Spain [47]	1004 people hospitalised for COPD exacerbations; two separate studies (ECCO and ESMI)	ECCO 29%, ESMI 37%	
Poland [48]	266 COPD patients who died during hospitalisation for exacerbation	21%	
Australia [49]	172 people hospitalised for COPD exacerbations	22%	
Italy [50]	316 COPD patients referred for pulmonary rehabilitation	12%	
Italy [51]	288 people hospitalised for COPD exacerbations	25%	
USA [52]	Commercial dataset 42565 COPD patients, Medicare dataset 8507 COPD patients	Commercial 22%, Medicare 29%	
Iceland [53]	416 people hospitalised for COPD exacerbations	11%	
Italy [54]	GP database, 1.5% of Italian population	19%	Diabetes less common in general population 11%
The Netherlands [55]	Patients recruited from general practice ≥ 40 years of age with (n=290) or without (n=421) diagnosis of asthma or COPD	5%	Diabetes more common in controls 7%
USA [56]	Medical Care Programme, 45966 COPD patients, equal number of matched controls	2%	Diabetes less common in controls (1%), OR (95% CI) for diabetes in COPD 1.51 (1.35–1.69)
USA [57]	Nurses' health study: 103614 female nurses		COPD risk factor for developing diabetes RR 1.8 (95% CI 1.1–2.8)
USA [58]	Female's health study: 38570 females aged >45 years, free of CVD/cancer at baseline		COPD RR for diabetes 1.38 (95% CI 1.14–1.67) after adjustment
USA [59]	Atherosclerosis risk in communities and cardiovascular health study: 20296 people >45 years of age		GOLD stage III or IV disease; OR for diabetes 1.5 (95% CI 1.1–1.9)
Korea [60]	Health and nutrition examination survey. General population ≥ 40 years of age: 2177 people. 14.1% patients had COPD		No association between COPD and diabetes
UK [61]	General practice database: 1204100 people		Physician diagnosis of COPD associated with increased risk of diabetes OR 2.04 (95% CI 1.97–2.12)

ECCO: EPOC con comorbilidad; ESMI: Enfermedad Pulmonar Obstructiva Crónica Servicio de Medicina Interna; GP: general practitioner; RR: risk ratio; CVD: cardiovascular disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

healthy age-matched controls and at 75% of the intensity [67]. COPD patients were also significantly physically inactive for longer periods of time than control participants (82% *versus* 68% of recording time, respectively) and spent more time seated or lying and less time standing than controls [68]. Several studies have shown a moderate correlation between daily physical activity and forced expiratory volume in 1 second (FEV₁) % predicted [67]. WATZ *et al.* [42] found an association between metabolic syndrome and physical inactivity in COPD, independent of lung function impairment.

Cigarette smoke

Tobacco smoke exposure is central to the development of COPD. Cigarette smoking is associated with increased waist–hip ratio, an indicator of increased visceral adipose tissue [69]. In euglycaemic clamp studies, smoking, but not snuffing, tobacco directly impaired insulin action and reduced peripheral glucose uptake [70]. Smokers had higher steady-state plasma glucose concentrations in response to a continuous infusion of glucose, insulin and somatostatin when compared with nonsmokers [71]. Smoking habits correlated with manifestations of the metabolic syndrome including low HDL cholesterol, high triglycerides and increased plasminogen activator inhibitor [72]. Epidemiological studies have shown a higher rate of metabolic syndrome and type 2 diabetes in smokers than in nonsmokers. For example in US adolescents, 1.2% of nonsmokers and 8.7% of smokers had metabolic syndrome [73]. The risk of diabetes is 70% greater in people who smoke >20 cigarettes per day [74]. Insulin resistance [75] and risk of diabetes [74] decrease with smoking cessation, although early benefits may be attenuated by weight gain.

Corticosteroids

Short-term oral corticosteroid treatment for acute COPD exacerbations is associated with a five-fold increased risk of acute hyperglycaemia [76]. Longer-term corticosteroid use in stable COPD is associated with increased risk of glucose intolerance [77]. The effects of oral corticosteroids on other aspects of metabolic syndrome in COPD have not been studied. However, metabolic syndrome is almost invariable in endogenous corticosteroid excess (Cushing's syndrome) [14]. Inhaled corticosteroid use in diabetic patients with airways disease was associated with a small increase in serum glucose [78], although this did not have a clinically significant impact on long-term glycaemic control as assessed by glycated haemoglobin (HbA_{1c}) [79]. However, in a large, randomised controlled trial, patients receiving inhaled budesonide 400 µg twice daily were no more likely than those receiving placebo to develop diabetes over 3 years of follow up [80].

Inflammation

Both COPD and metabolic syndrome/type 2 diabetes are associated with systemic inflammation, which drives insulin resistance, atherosclerosis and other systemic manifestations of COPD. Coexistence of COPD and metabolic syndrome/type 2 diabetes could, therefore, potentiate systemic inflammation, exacerbating both conditions. In support of this, systemic inflammation is more severe in COPD patients with metabolic syndrome at all GOLD stages [42, 43, 81]. COPD disease severity and metabolic syndrome, as well as physical inactivity, were independent predictors of systemic inflammation measured by high-sensitivity C-reactive protein (hs-CRP) and IL-6 [42]. Metabolic syndrome and type 2 diabetes are also more common in other chronic inflammatory diseases, such as psoriasis [82] and inflammatory arthritides [83]. Interestingly, in rheumatoid arthritis, anti-inflammatory therapy with anti-TNF agents improved insulin resistance, reduced serum triglycerides and increased serum HDL cholesterol [84].

Oxidative stress

Oxidative stress is increased by cigarette smoking and in patients with COPD when stable or during acute exacerbations [85]. It is also increased in metabolic syndrome/type 2 diabetes by activation of biochemical pathways, with increased delivery of reactive oxygen species, decreased antioxidant protection and increased lipid peroxidation [8]. Oxidative stress generated by smoking/COPD could drive metabolic syndrome/type 2 diabetes by perpetuating insulin resistance and altering energy production [8]. Conversely oxidative stress generated by metabolic syndrome/type 2 diabetes could worsen COPD by activating inflammation and impairing therapeutic response to glucocorticoids [86].

Hypoxia

Hypoxia imposes strong metabolic demands, requiring a shift in fuel preference to glucose at the expense of fatty acid oxidation [87]. In healthy volunteers at high altitude, increased hepatic insulin resistance and glucose production [88] is accompanied by increased peripheral insulin sensitivity and glucose uptake into skeletal muscle [89]. Blood glucose concentrations are lower at

high altitude than at sea level [90]. People with type 2 diabetes and metabolic syndrome visiting high altitude experienced improvement in blood glucose control and metabolic profiles [91, 92]. By contrast, high-altitude dwellers were more likely to have metabolic syndrome than sea-level dwellers [93]. COPD patients with chronic hypoxia have impaired glucose tolerance [94] and increased lipolysis with reduced insulin sensitivity [95]. Normalisation of oxygen saturations in COPD improves glucose tolerance and tissue sensitivity to insulin [96].

Impact of metabolic syndrome and diabetes in COPD

In people with COPD, coexisting metabolic syndrome and diabetes are associated with increased morbidity and mortality, impaired lung function and increased respiratory exacerbations. A potential effect of metabolic syndrome and diabetes on COPD comorbidities, including skeletal muscle dysfunction, osteoporosis, cancer risk, depression and cognitive impairment can be inferred from studies in other patient groups.

Mortality

There are no studies that directly determine the relationship between metabolic syndrome and survival in COPD. However, metabolic syndrome predisposes to cardiovascular disease which affects 20%–22% COPD patients and is associated with significantly increased risk of death over 5 years [59].

Patients with coexisting COPD and diabetes have an increased risk of death compared with those with either condition alone. COPD patients with diabetes are more than twice as likely to die as those without diabetes in the 24 months following hospitalisation for an exacerbation [53]. COPD confers a 27% higher risk of death when it coexists with diabetes [97].

Respiratory disease

Lung function

In population studies, metabolic syndrome and diabetes are associated with decreased vital capacity in a restrictive pattern, after correction for smoking and other confounding factors [98]. Underlying mechanisms include increased inflammation, mechanical and other effects of abdominal obesity [99].

Lung diffusion capacity is reduced in people with diabetes, with the reduction being greatest in those with microvascular complications [100]. Using electron microscopy, alveolar epithelial and endothelial capillary basal laminar thickening can be seen in the lungs of people with diabetes [101]. Pulmonary microvascular disease may contribute to respiratory impairment in patients with COPD and diabetes.

Exacerbations

A single study has investigated the association between metabolic syndrome and COPD exacerbations [40]. The study found that 29 COPD patients with metabolic syndrome had more exacerbations over the subsequent year of follow-up (mean $\pm$ SD 2.4 ± 0.8 exacerbations) than 77 patients without metabolic syndrome matched for lung function (0.7 ± 0.6 exacerbations). Exacerbation duration was longer in patients with metabolic syndrome (7.5 ± 1.5 days) than in those without (5.0 ± 2.4 days). Exacerbation frequency was positively correlated with baseline CRP, as well as with triglycerides and blood glucose, indicating that increased inflammation and/or the proinfective/immune suppressant effects of hyperglycaemia could be contributing mechanisms.

COPD patients with diabetes have an increased risk of hospitalisation [59], more gram negative organisms cultured from sputum during exacerbation [102], and require longer stays in hospital if admitted than those without diabetes [49, 102]. At hospital admission, 50% of COPD patients develop acute hyperglycaemia [103, 104]. Acute hyperglycaemia during exacerbation is associated with an increased risk of death, prolonged hospital stay, multiple pathogens on sputum culture [103]

and failure of noninvasive ventilation (NIV) [104]. Multiple mechanisms, including the pro-inflammatory and pro-inflammatory effects of hyperglycaemia, impaired immunity and skeletal muscle dysfunction, are thought to play a role [105]. Hyperglycaemia may also enhance the responsiveness of airway smooth muscle to contractile agents [106].

Comorbidities

Skeletal muscle

Skeletal muscle weakness is more common in people with COPD (32%) than in age-matched controls (8%) [107]. Over 1 year, skeletal muscle strength declines by 4.3% in COPD patients, compared with 1–2% in a healthy ageing population [108]. Skeletal muscle wasting in COPD is a significant determinant of mortality [41, 109], poor health status, increased healthcare utilisation [110], hospitalisation and need for mechanical ventilatory support.

COPD patients with diabetes undertake less physical activity [111] and respond less well to pulmonary rehabilitation [50] when compared to those without. There is no direct research into the contribution of metabolic syndrome/type 2 diabetes to skeletal muscle decline in COPD. However, people with type 2 diabetes without COPD have decreased upper and lower limb muscle strength [112] and faster loss of muscle strength [113] than people without diabetes. Longer duration of diabetes and poor glycaemic control are associated with worse muscle function [112]. Diabetes is associated with a two- to three-times increased risk of developing physical disability [114] and of injurious falls [115].

Insulin resistance may be an important mechanism in the development of skeletal muscle weakness and wasting in COPD patients with metabolic syndrome/type 2 diabetes. Insulin is an important anabolic hormone, stimulating post-prandial protein synthesis in skeletal muscle [116]. Insulin resistance is associated with increased skeletal muscle protein breakdown in nondiabetic patients requiring haemodialysis [117] and in critically ill patients [118]. Insulin acts as a major regulator of mitochondrial oxidative phosphorylation in human skeletal muscle [119], a process that generates adenosine triphosphate (ATP), which is essential for muscle contraction and other cellular activities. Insulin resistance is associated with mitochondrial dysfunction [120]. People with type 2 diabetes have reduced stimulation of mitochondrial ATP production by insulin, indicating that insulin resistance may limit mitochondrial activity and impair fuel metabolism regulation in skeletal muscle [119]. Other mechanisms that could cause skeletal muscle wasting and dysfunction in metabolic syndrome and diabetes include inflammation [113], altered muscle blood flow or neuropathy.

Bone metabolism and vitamin D

17–47% people with COPD have osteoporosis and 21–53% have metabolic syndrome [121, 122]. Although there are no specific studies involving the association between osteoporosis and metabolic syndrome in COPD, the two conditions are likely to be linked at least by common risk factors, such as smoking, physical inactivity and corticosteroid treatment. Components of the metabolic syndrome, particularly hypertension, increased triglycerides and reduced HDL cholesterol are risk factors for low bone-mineral density, and features of the metabolic syndrome, such as inflammation, play a role in the pathogenesis of osteoporosis [123]. However, population studies of the association between metabolic syndrome and osteoporosis have produced conflicting results, due to the confounding protective effects of obesity.

The majority of COPD patients have vitamin D deficiency [124], which, in over 40 separate studies, has been associated with increased risk of metabolic syndrome or with increased incidence or severity of its components [125]. There is some evidence from prospective trials that vitamin D supplementation at levels recommended for bone protection could prove protective against metabolic syndrome [125].

Cancer

Both COPD [121] and metabolic syndrome [24] are associated with an increased risk of cancer, although it is not known whether the cancer risk is increased further in people who have both

conditions. Chronic inflammation may play a significant role in the pathogenesis of cancer as a tumour promoter [126]. Inflammatory mediators can inhibit apoptosis, interfere with cellular repair and promote angiogenesis, enhancing both tumour growth and metastasis [126].

Depression

The prevalence of depression in COPD patients is 10–79% [127]. While mechanisms underlying COPD-related depression are undoubtedly complex, there is some evidence from other patient groups that metabolic syndrome could play a role. In a recent large meta-analysis, people with metabolic syndrome were 27% more likely to have depression and 41% more likely to develop depression than those without [25]. In a separate study, age, fasting glucose and hs-CRP were independently associated with depressive symptoms, indicating that inflammation could play a role [128]. Pioglitazone, a thiazolidinedione with insulin-sensitising, anti-inflammatory and neuroprotective properties, increased treatment response, remission and early improvement of symptoms when given as adjuvant treatment with citalopram for patients with major depressive disorder [129].

Cognition

19% of people aged ≥ 45 years with COPD reported memory problems [121]. In-depth cognitive function testing identifies a specific pattern of cognitive impairment with COPD, with deficits in areas that include attention, memory and executive function [127]. While mechanisms including hypoxia, smoking and vascular disease are important contributors to cognitive decline in COPD, metabolic syndrome may also play a role. In cross-sectional population studies, metabolic syndrome was independently associated with cognitive impairment [26, 27], except in those aged >80 years [130]. Affected cognitive domains included information processing speed, attention and executive functioning [131]. In longitudinal studies, metabolic syndrome was a risk factor for accelerated cognitive decline in females [132]. Possible mechanisms include impaired brain energy metabolism and disruption of hippocampal insulin signalling.

Implications for treatment

The strong association between COPD, metabolic syndrome and type 2 diabetes can be explained by common risk factors and pathological mechanisms. Coexistence of these conditions increases the severity and impact of each, worsening patient outcomes. Best clinical practice should, therefore, include both optimisation of respiratory disease to reduce insulin resistance and control of blood glucose and other metabolic factors to improve respiratory disease, reduce cardiovascular risk and, possibly, to improve other systemic manifestations. Smoking cessation and pulmonary rehabilitation already have combined benefits for both respiratory and metabolic disease. Modifications to exercise regimens, nutritional advice and pharmacotherapy, aimed at reducing risk or improving control of metabolic syndrome and diabetes, could further improve outcomes for all COPD patients.

Exercise

Current international guidelines for pulmonary rehabilitation in COPD all recommend inclusion of aerobic exercise training to improve exercise tolerance and quality of life [133]. Greater intensity, duration and frequency of exercise training are associated with greater benefits. There is less consensus about the inclusion of resistance training, although this is recognised to improve muscle mass and strength.

Breaks in sedentary time

For metabolic syndrome and diabetes, any movement is better than no movement. Increased breaks in sedentary time were beneficially associated with waist circumference, BMI, triglycerides, 2-hour plasma glucose and CRP, independent of total sedentary time and potential confounders [134].

Aerobic exercise

In patients with cardiometabolic disorders, continuous moderate-intensity aerobic exercise, (60–75% maximal heart rate) and aerobic interval training (high-intensity (85%–95% maximal heart rate) bouts separated by moderate- or low-intensity active recovery) for approximately 30 minutes three-times a week reduced body weight, waist circumference and blood pressure to a similar extent [135]. Aerobic interval training caused a significantly greater reduction in fasting plasma glucose [136], but neither intervention improved dyslipidaemia [135–137].

Resistance training

Resistance training is any activity that causes muscles to contract against external force. Progressive resistance training both increases skeletal muscle mass and changes the metabolic function of skeletal muscle fibres. This has the effect of increasing insulin sensitivity and glucose utilisation in peripheral muscle, improving glucose tolerance. In type 2 diabetes, resistance training lowered HbA_{1c} by up to 18%, to a greater extent than that seen with aerobic training [138]. Resistance training also appears to reduce low-density lipoprotein (LDL) cholesterol by 5–23% [139]. However, the combination of aerobic and resistance activity has the greatest benefit on plasma lipid profile, both lowering LDL and raising HDL cholesterol [140].

Implications for COPD

Aerobic training as performed in standard pulmonary rehabilitation programmes is sufficient to have metabolic benefits for COPD patients. Evidence from the cardiometabolic literature provides additional support for inclusion of strength/resistance training as part of the exercise programme. COPD patients who are unwilling or unable to participate in these programmes should at least be encouraged to get up regularly and avoid prolonged periods of sitting.

Weight management and nutrition

Nutritional advice and maintenance of optimal body weight are recognised as important in COPD, but there are few recommendations on how this should be done [133]. As low BMI is an independent risk factor for mortality in COPD patients, most recommendations are focussed on maintaining weight in patients with cachexia [133]. In overweight COPD patients, nutritional advice to control weight and improve metabolism is important in order to reduce the prevalence and impact of metabolic syndrome and type 2 diabetes.

Weight management

In addition to exercise, the most effective way to prevent or improve control of metabolic syndrome/type 2 diabetes is through weight loss and the reduction in abdominal obesity. In morbidly obese patients, dramatic weight loss, achieved by bariatric surgery, resulted in the resolution of metabolic syndrome and reduced insulin resistance, reducing progression to or improving control of type 2 diabetes [141]. In COPD, there is an “obesity paradox”, in which overweight and obese patients have a better prognosis than those with low or normal body weight [142]. It is, therefore, not known whether weight loss will improve or worsen outcomes in this patient group. However, dietary modification has potential to increase insulin sensitivity and reduce cardiovascular risk, independent of weight loss.

Nutrition

Basic dietary advice for avoidance or control of the metabolic syndrome/type 2 diabetes should include: control of calorie intake to maintain (or lose) weight; balance of carbohydrate, fat and protein intake (approximately 40%, 30% and 30%, respectively); increased consumption of complex carbohydrates with low glycaemic index and soluble fibre; and avoidance of saturated fat [143, 144]. Table 3 gives a more detailed summary of the beneficial and detrimental effects of diverse nutrients on components of the metabolic syndrome.

Table 3. Influence of dietary constituents on metabolic syndrome

	Beneficial effects	Detrimental effects
Insulin resistance	Low glycaemic index carbohydrates [#] Soluble fibre [†] Increased meal frequency (isocaloric) Soy protein	High glycaemic index carbohydrates Fructose Saturated fat
Abdominal obesity	Whole grains Fibre rich diet Hypocaloric intake	Hypercaloric intake Alcohol excess
Serum triglycerides	Long-chain omega-3 fatty acids ⁺ Low glycaemic index carbohydrates Soy protein	Trans fatty acids [§]
Serum HDL cholesterol	Low glycaemic index carbohydrates Moderate alcohol consumption (five to seven drinks per week) Extra virgin olive oil Soy protein	High carbohydrate intake Trans fatty acids
Serum LDL cholesterol	Soluble fibre Extra virgin olive oil Soy protein	Trans fatty acids
Blood pressure		Salt
Inflammation	Long chain omega 3 fatty acids Moderate alcohol consumption (five to seven drinks per week) Extra virgin olive oil ^f Whole grains	
Oxidative stress	Extra virgin olive oil	

HDL: high-density lipoprotein; LDL: low-density lipoprotein. [#]: glycaemic index is a measure of the change in blood glucose in response to carbohydrate consumption. Low glycaemic index foods, such as fruits, vegetables, whole grains and nuts, release glucose slowly and steadily after a meal. This reduces post-prandial glucose concentrations, with beneficial effects on oxidative and glycative stress and insulin levels. [†]: soluble fibre is readily fermented in the colon into gases and physiologically active by-products. This is thought to exert beneficial effects on insulin resistance through modification of appetite and effects on gut peptides, influencing glucose homeostasis. Good sources of soluble fibre include peas, beans, nuts and seeds, oats, root and other vegetables, and some fruits. ⁺: long-chain omega-3 fatty acids. Long chain eicosapentaenoic and docosahexaenoic acids have proven cardioprotective effects, whereas the health benefits of short-chain omega-3 fatty acids, such as α -linoleic acid, are unproven. [§]: trans fatty acids are found in processed foods, including baked products and snacks. ^f: extra virgin olive oil is unrefined, so contains high concentrations of phenolic compounds which have beneficial metabolic effects. Olive oil that is not "extra virgin" is refined and these compounds are removed; therefore, it does not have these properties. Data taken from [142, 143].

Pharmacotherapy

Pharmacological approaches include increasing insulin sensitivity to prevent or control metabolic syndrome and diabetes and reduction in cardiovascular risk by addressing individual risk factors, particularly dyslipidaemia and hypertension.

Increasing insulin sensitivity

Control of respiratory disease

Inflammation increases insulin resistance and metabolic dysfunction. In rheumatoid arthritis, anti-inflammatory therapy reduced insulin resistance, reduced serum triglycerides and increased serum HDL-cholesterol [84]. In COPD, metabolic syndrome is associated with increased number and duration of exacerbations [40]. More research is required to determine whether prevention or prompt treatment of exacerbations can reduce insulin resistance and improve metabolic syndrome in COPD.

Medication review

Corticosteroid excess causes insulin resistance, metabolic syndrome and diabetes [14]. Long-term oral corticosteroid use has no proven benefits in COPD [77] and so should be avoided or stopped to minimise metabolic impact. Inhaled corticosteroids do not appear to increase insulin resistance significantly [79, 80]. Nonrespiratory medication, including antipsychotic drugs [12] and older generation beta blockers [13] that increase insulin resistance, could be substituted with alternatives that cause less metabolic disturbance.

Vitamin D

Vitamin D levels should be tested in all COPD patients and supplemented in those with deficiency at levels recommended for bone protection. There is some evidence that this could also reduce insulin resistance and protect against metabolic syndrome [125].

Drugs that increase insulin sensitivity

Drugs that increase insulin sensitivity improve glycaemic control in type 2 diabetes. They may also prevent new-onset diabetes in high-risk patients and improve other components of the metabolic syndrome. There is currently no evidence to inform use of these drugs in COPD patients without diabetes. As this field develops, it should be noted that patients who take drugs to reduce insulin resistance as a preventative measure have a high likelihood of glycaemic rebound if treatment is stopped [145].

Metformin is a biguanide that improves glucose tolerance by increasing insulin sensitivity. Metformin reduces the incidence of newly diagnosed diabetes in people with impaired glucose tolerance by 31%, particularly in younger, obese patients [145]. Metformin also reduces weight and HbA_{1c}, improves dyslipidaemia and has anti-inflammatory and anti-thrombotic effects [146]. These additional properties may explain why metformin reduces cardiovascular risk to a greater extent than would be expected from its blood glucose lowering actions alone [147].

Thiazolidinediones (glitazones) activate peroxisome proliferator-activated receptors (PPARs), increasing insulin sensitivity through changes in gene transcription. Rosiglitazone reduces the risk of progression of impaired glucose tolerance to diabetes by 60% [145]. Although thiazolidinediones can cause weight gain, they reduce HbA_{1c} and blood pressure control, improve dyslipidaemia and have anti-inflammatory and anti-thrombotic properties [146].

Acarbose inhibits the enzyme α -glucosidase in the small intestine, delaying the digestion of complex carbohydrates. It reduces the incidence of newly diagnosed diabetes in people with impaired glucose tolerance by 36% [145]. Furthermore, it reduces weight, HbA_{1c}, triglycerides and total cholesterol and reduced thrombus formation in animal studies [146].

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blocking drugs (ARBs) increase insulin sensitivity, with improvements in insulin signalling being mediated by increased bradykinin and decreased angiotensin II activity [148]. In retrospective studies, ACEI and ARBs reduced new-onset diabetes in high-risk patients by 20%–34% [148]. In prospective studies, ramipril (an ACEI) increased regression of impaired glucose tolerance to normoglycaemia but did not significantly reduce the incidence of new-onset diabetes. Valsartan (an ARB) reduced the incidence of new-onset diabetes by 14% [148]. As ACEI/ARBs also lower blood pressure and improve dyslipidaemia, they have additional beneficial effects for metabolic syndrome as a whole [149].

Reducing cardiovascular risk

Management of dyslipidaemia

Increased total and LDL cholesterol are the major risk factors for cardiovascular disease, with low HDL and high triglycerides seen in metabolic syndrome being additional independent risk factors [150]. The first-line treatment for dyslipidaemia is, therefore, statin therapy, which principally

lowers LDL and total cholesterol, with smaller effects on other lipids. Targets for cholesterol-lowering treatment vary depending on calculated risk of cardiovascular disease. In people at low risk of cardiovascular disease, total cholesterol should be less than 5 mmol·L⁻¹ and LDL cholesterol should be less than 3 mmol·L⁻¹. However, LDL cholesterol targets are as low as 1.8 mmol·L⁻¹ in people at high risk of cardiovascular disease. Statins have recently been shown to increase the risk of diabetes, particularly in people with metabolic syndrome, obesity and impaired glucose tolerance [151]. However this should not prevent their use in patients at high risk of cardiovascular disease. In metabolic syndrome, combining nicacin with a statin or using fibrates can further increase HDL cholesterol and reduce triglycerides [150].

Management of hypertension

Blood pressure should be controlled to systolic, less than 140 mmHg, and diastolic, less than 90 mmHg, in all patients [150]. There may be additional benefits from further blood pressure reduction, but this is not consistently supported by trial evidence [150]. Although there is no significant difference in blood pressure-lowering efficacy between major antihypertensive drug classes, ACEI and ARB may improve insulin sensitivity in metabolic syndrome and reduce nephropathy in diabetes. Beta blockers and diuretics increase the risk of new-onset diabetes in people with multiple metabolic risk factors.

Conclusion

Metabolic syndrome and type 2 diabetes are 1.5–3 times more common in COPD than in the general population. This association is accounted for by common risk factors, such as smoking; consequences of COPD, including inactivity, obesity and systemic inflammation; and corticosteroid treatment, all of which increase insulin resistance. COPD patients with metabolic syndrome/diabetes have increased systemic inflammation, which may contribute to increased mortality and more frequent and prolonged respiratory exacerbations seen in people with both conditions. Insulin resistance and metabolic disturbance may also contribute to other systemic manifestations of COPD, including skeletal muscle wasting, depression and cognitive decline. Modification of standard exercise programmes, nutritional advice and pharmacotherapy in COPD has potential to improve outcomes for COPD patients by reducing insulin resistance and cardiovascular risk.

Statement of Interest

None declared.

References

1. Alberti KGMM, Eckel RH, Grundy SM, *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640–1645.
2. Krebs M, Roden M. Molecular mechanisms of lipid-induced insulin resistance in muscle, liver and vasculature. *Diabetes Obes Metab* 2005; 7: 621–632.
3. Cornier MA, Dabelea D, Hernandez TL, *et al.* The metabolic syndrome. *Endocr Rev* 2008; 29: 777–822.
4. Romeo GR, Lee J, Shoelson SE Metabolic syndrome, insulin resistance, and roles of inflammation--mechanisms and therapeutic targets. *Arterioscler Thromb Vasc Biol* 2012; 32: 1771–1776.
5. Emanuelli B, Peraldi P, Filloux C, *et al.* SOCS-3 inhibits insulin signalling and is up-regulated in response to tumor necrosis factor- α in the adipose tissue of obese mice. *J Biol Chem* 2001; 276: 47944–47949.
6. Cai D, Yuan M, Frantz DF, *et al.* Local and systemic insulin resistance resulting from hepatic activation of IKK- β and NF- κ B. *Nat Med* 2005; 11: 183–190.
7. Palomo I, Alarcón M, Moore-Carrasco R, *et al.* Hemostasis alterations in metabolic syndrome. *Int J Mol Med* 2006; 18: 969–974.
8. Grattagliano I, Palmieri VO, Portincasa P, *et al.* Oxidative stress-induced risk factors associated with the metabolic syndrome: a unifying hypothesis. *J Nutr Biochem* 2008; 19: 491–504.

9. Norris JM, Rich SS. Genetics of glucose homeostasis: implications for insulin resistance and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2012; 32: 2091–2096.
10. Iijima K, Iimuro S, Ohashi Y, *et al.* Lower physical activity, but not excessive calorie intake, is associated with metabolic syndrome in elderly with type 2 diabetes mellitus: The Japanese Elderly Diabetes Intervention Trial. *Geriatr Gerontol Int* 2012; 12: Suppl. 1, 68–76.
11. Hester EK. HIV medications: an update and review of metabolic complications. *Nutr Clin Pract* 2012; 27: 51–64.
12. De Hert M, Detraux J, van Winkel R, *et al.* Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2011; 8: 114–126.
13. Carella AM, Antonucci G, Conte M, *et al.* Antihypertensive treatment with beta-blockers in the metabolic syndrome: a review. *Curr Diabetes Rev* 2010; 6: 215–221.
14. Chanson P, Salenave S. Metabolic syndrome in Cushing's syndrome. *Neuroendocrinol* 2010; 92: Suppl. 1, 96–101.
15. Kassi E, Pervanidou P, Kaltsas G, *et al.* Metabolic syndrome: definitions and controversies. *BMC Med* 2011; 9: 48.
16. Sumner AD, Khalil YK, Reed JF 3rd. The relationship of peripheral arterial disease and metabolic syndrome prevalence in asymptomatic US adults 40 years and older: results from the National Health and Nutrition Examination Survey (1999–2004). *J Clin Hypertens (Greenwich)* 2012; 14: 144–148.
17. Chang JJ, Chu CM, Wang PC, *et al.* Differences in prevalence and severity of coronary artery disease by three metabolic syndrome definitions. *Can J Cardiol* 2012; 28: 208–214.
18. Rachas A, Raffaitin C, Barberger-Gateau P, *et al.* Clinical usefulness of the metabolic syndrome for the risk of coronary heart disease does not exceed the sum of its individual components in older men and women. The Three-City (3C) Study. *Heart* 2012; 98: 650–655.
19. McNeill AM, Rosamond WD, Gorman CJ, *et al.* The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care* 2005; 28: 385–390.
20. Tziomalos K, Athyros VG, Karagiannis A, *et al.* Endothelial dysfunction in metabolic syndrome: prevalence, pathogenesis and management. *Nutr Metab Cardiovasc Dis* 2010; 20: 140–146.
21. Mathieu P, Pibarot P, Després JP. Metabolic syndrome: the danger signal in atherosclerosis. *Vasc Health Risk Manag* 2006; 2: 285–302.
22. Atlantis E, Martin SA, Haren MT, *et al.* Inverse associations between muscle mass, strength, and the metabolic syndrome. *Metabolism* 2009; 58: 1013–1022.
23. Hwang DK, Choi HJ. The relationship between low bone mass and metabolic syndrome in Korean women. *Osteoporos Int* 2010; 21: 425–431.
24. Chen W, Lu F, Liu SJ, *et al.* Cancer risk and key components of metabolic syndrome: a population-based prospective cohort study in Chinese. *Chin Med J (Engl)* 2012; 125: 481–485.
25. Pan A, Keum N, Okereke OI, *et al.* Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care* 2012; 35: 1171–1180.
26. Viscogliosi G, Andreozzi P, Chiriac IM, *et al.* Screening cognition in the elderly with metabolic syndrome. *Metab Syndr Relat Disord* 2012; 10: 358–362.
27. Vieira JR, Elkind MS, Moon YP, *et al.* The metabolic syndrome and cognitive performance: the Northern Manhattan Study. *Neuroepidemiology* 2011; 37: 153–159.
28. World Health Organisation. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: report of a WHO/IDF consultation. 2006 www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf Date last updated: 2006. Date last accessed: January 9, 2013.
29. Lorenzo C, Williams K, Hunt KJ, *et al.* The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007; 30: 8–13.
30. Bierman EL. George Lyman Duff Memorial Lecture. Atherogenesis in diabetes. *Arterioscler Thromb Vasc Biol* 1992; 12: 647–656.
31. Cusi K. The role of adipose tissue and lipotoxicity in the pathogenesis of type 2 diabetes. *Curr Diab Rep* 2010; 10: 306–315.
32. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol* 2012; 59: 635–643.
33. Nathan DM, Davidson MB, DeFronzo RA, *et al.* Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007; 30: 753–759.
34. Koh GC, Peacock SJ, van der Poll T, *et al.* The impact of diabetes on the pathogenesis of sepsis. *Eur J Clin Microbiol Infect Dis* 2012; 31: 379–388.
35. Brennan AL, Gyi KM, Wood DM, *et al.* Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. *J Cyst Fibros* 2007; 6: 101–109.
36. Brennan AL, Baines DL, Woollhead A, *et al.* Development of an *in vitro* model to investigate the effect of glucose on the interaction between respiratory epithelia and bacterial pathogens. *Thorax* 2006; 61: Suppl. 2, ii101.
37. Esposito K, Nappo F, Marfella R, *et al.* Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 2002; 106: 2067–2072.
38. Park BH, Park MS, Chang J, *et al.* Chronic obstructive pulmonary disease and metabolic syndrome: a nationwide survey in Korea. *Int J Tuberc Lung Dis* 2012; 16: 694–700.

39. Minas M, Kostikas K, Papaioannou AI, *et al.* The association of metabolic syndrome with adipose tissue hormones and insulin resistance in patients with COPD without co-morbidities. *COPD* 2011; 8: 414–420.
40. K peli E, Ulubay G, Ulasli SS, *et al.* Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study. *Endocrine* 2010; 38: 76–82.
41. Marquis K, Debigare R, Lacasse Y, *et al.* Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 809–813.
42. Watz H, Waschki B, Kirsten A, *et al.* The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009; 136: 1039–1046.
43. Poulain M, Doucet M, Drapeau V, *et al.* Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. *Chron Respir Dis* 2008; 5: 35–41.
44. Funakoshi Y, Omori H, Mihara S, *et al.* Association between airflow obstruction and the metabolic syndrome or its components in Japanese men. *Intern Med* 2010; 49: 2093–2099.
45. Lam KB, Jordan RE, Jiang CQ, *et al.* Airflow obstruction and metabolic syndrome: the Guangzhou Biobank Cohort Study. *Eur Respir J* 2010; 35: 317–323.
46. Chang C, Yao WZ, Fang TS. [Incidence of comorbidities in hospitalized chronic obstructive pulmonary disease patients and correlated risk factors.] *Zhonghua Yi Xue Za Zhi* 2012; 92: 943–947.
47. Almagro P, L pez F, Cabrera FJ, *et al.* [Comorbidities in patients hospitalized due to chronic obstructive pulmonary disease. A comparative analysis of the ECCO and ESMI studies.] *Rev Clin Esp* 2012; 212: 281–286.
48. Rubinsztajn R, Chazan R. [Mortality and comorbidity in hospitalized chronic obstructive pulmonary disease patients.] *Pneumonol Alergol Pol* 2011; 79: 343–346.
49. Parappil A, Depczynski B, Collett P, *et al.* Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. *Respirology* 2010; 15: 918–922.
50. Crisafulli E, Costi S, Luppi F, *et al.* Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. *Thorax* 2008; 63: 487–492.
51. Terzano C, Conti V, Di Stefano F, *et al.* Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study. *Lung* 2010; 188: 321–329.
52. Mapel DW, Duto MP, Marton JP, *et al.* Identifying and characterizing COPD patients in US managed care. A retrospective, cross-sectional analysis of administrative claims data. *BMC Health Serv Res* 2011; 11: 43.
53. Gudmundsson G, Gislason T, Lindberg E, *et al.* Mortality in COPD patients discharged from hospital: the role of treatment and co-morbidity. *Respir Res* 2006; 7: 109.
54. Cazzola M, Bettoncelli G, Sessa E, *et al.* Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration* 2010; 80: 112–119.
55. van Manen JG, Bindels PJ, IJzermans CJ, *et al.* Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol* 2001; 54: 287–293.
56. Sidney S, Sorel M, Quesenberry CP Jr, *et al.* COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005; 128: 2068–2075.
57. Rana JS, Mittleman MA, Sheikh J, *et al.* Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27: 2478–2484.
58. Song Y, Klevak A, Manson JE, *et al.* Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the Women's Health Study. *Diabetes Res Clin Pract* 2010; 90: 365–371.
59. Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962–969.
60. Joo H, Park J, Lee SD, *et al.* Comorbidities of chronic obstructive pulmonary disease in Koreans: a population-based study. *J Korean Med Sci* 2012; 27: 901–906.
61. Feary JR, Rodrigues LC, Smith CJ, *et al.* Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010; 65: 956–962.
62. Steuten LM, Creutzberg EC, Vrijhoef HJ, *et al.* COPD as a multicomponent disease: inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care. *Prim Care Respir J* 2006; 15: 84–91.
63. Schokker DF, Visscher TL, Nooyens AC, *et al.* Prevalence of overweight and obesity in the Netherlands. *Obes Rev* 2007; 8: 101–108.
64. Eisner MD, Blanc PD, Sidney S, *et al.* Body composition and functional limitation in COPD. *Respir Res* 2007; 8: 7.
65. Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Data. Atlanta, US Department of Health and Human Services, Centers for Disease Control and Prevention 2012. Available from <http://www.cdc.gov/brfss/>.
66. Skyba P, Ukropec J, Pobeha P, *et al.* Metabolic phenotype and adipose tissue inflammation in patients with chronic obstructive pulmonary disease. *Mediators Inflamm* 2010; 2010: 173498.
67. Vorrink SN, Kort HS, Troosters T, *et al.* Level of daily physical activity in individuals with COPD compared with healthy controls. *Respir Res* 2011; 12: 33.
68. Coronado M, Janssens JP, de Muralt B, *et al.* Walking activity measured by accelerometry during respiratory rehabilitation. *J Cardiopulm Rehabil* 2003; 23: 357–364.

69. Canoy D, Wareham N, Luben R, *et al.* Cigarette smoking and fat distribution in 21,828 British men and women: a population-based study. *Obes Res* 2005; 13: 1466–1475.
70. Attvall S, Fowelin J, Lager I, *et al.* Smoking induces insulin resistance—a potential link with the insulin resistance syndrome. *J Intern Med* 1993; 233: 327–332.
71. Facchini FS, Hollenbeck CB, Jeppesen J, *et al.* Insulin resistance and cigarette smoking. *Lancet* 1992; 339: 1128–1130.
72. Eliasson B, Attvall S, Taskinen MR, *et al.* The insulin resistance syndrome in smokers is related to smoking habits. *Arterioscler Thromb Vasc Biol* 1994; 14: 1946–1950.
73. Weitzman M, Cook S, Auinger P, *et al.* Tobacco smoke exposure is associated with the metabolic syndrome in adolescents. *Circulation* 2005; 112: 862–869.
74. Manson JE, Ajani UA, Liu S, *et al.* A prospective study of cigarette smoking and the incidence of diabetes mellitus among U.S. male physicians. *Am J Med* 2000; 109: 538–542.
75. Eliasson B, Attvall S, Taskinen MR, *et al.* Smoking cessation improves insulin sensitivity in healthy middle-aged men. *Eur J Clin Invest* 1997; 27: 450–456.
76. Walters JA, Gibson PG, Wood-Baker R, *et al.* Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009; 1: CD001288.
77. Walters JAE, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 3: CD005374.
78. Slatore CG, Bryson CL, Au DH. The association of inhaled corticosteroid use with serum glucose concentration in a large cohort. *Am J Med* 2009; 122: 472–478.
79. Faul JL, Wilson SR, Chu JW, *et al.* The effect of an inhaled corticosteroid on glucose control in type 2 diabetes. *Clin Med Res* 2009; 7: 14–20.
80. Pauwels RA, Löfdahl CG, Laitinen LA, *et al.* Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999; 340: 1948–1953.
81. Stanciu S, Marinescu R, Iordache M, *et al.* Are systemic inflammatory profiles different in patients with COPD and metabolic syndrome as compared to those with COPD alone? *Respir Res* 2006; 7: 109.
82. Takahashi H, Iizuka H. Psoriasis and metabolic syndrome. *J Dermatol* 2012; 39: 212–218.
83. Santos MJ, Fonseca JE. Metabolic syndrome, inflammation and atherosclerosis - the role of adipokines in health and in systemic inflammatory rheumatic diseases. *Acta Reumatol Port* 2009; 34: 590–598.
84. Stgakis I, Bertsias G, Karvounaris S, *et al.* Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. *Arthritis Res Ther* 2012; 14: R141.
85. Rahman I, Morrison D, Donaldson K, *et al.* Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med* 1996; 154: 1055–1060.
86. Chung KF, Adcock IM. Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *Eur Respir J* 2008; 31: 1334–1356.
87. Ge RL, Simonson TS, Cooksey RC, *et al.* Metabolic insight into mechanisms of high-altitude adaptation in Tibetans. *Mol Genet Metab* 2012; 106: 244–247.
88. Sauerwein HP, Schols AM. Glucose metabolism in chronic lung disease. *Clin Nutr.* 2002; 21: 367–371.
89. Gamboa JL, Garcia-Cazarin ML, Andrade FH. Chronic hypoxia increases insulin-stimulated glucose uptake in mouse soleus muscle. *Am J Physiol Regul Integr Comp Physiol* 2011; 300: R85–R91.
90. Castillo O, Woolcott OO, Gonzales E, *et al.* Residents at high altitude show a lower glucose profile than sea-level residents throughout 12-hour blood continuous monitoring. *High Alt Med Biol* 2007; 8: 307–311.
91. de Mol P, Fokkert MJ, de Vries ST, *et al.* Metabolic effects of high altitude trekking in patients with type 2 diabetes. *Diabetes Care* 2012; 35: 2018–2020.
92. Schobersberger W, Schmid P, Lechleitner M, *et al.* Austrian Moderate Altitude Study 2000 (AMAS 2000). The effects of moderate altitude (1,700 m) on cardiovascular and metabolic variables in patients with metabolic syndrome. *Eur J Appl Physiol* 2003; 88: 506–514.
93. Baracco R, Mohanna S, Seclén S. A comparison of the prevalence of metabolic syndrome and its components in high and low altitude populations in Peru. *Metab Syndr Relat Disord* 2007; 5: 55–62.
94. Hjalmarson A, Aasebo U, Birkeland K, *et al.* Impaired glucose tolerance in patients with chronic hypoxic pulmonary disease. *Diabetes Metab* 1996; 22: 37–42.
95. Jakobsson P, Jorfeldt L, von Schenck H. Fat metabolism and its response to infusion of insulin and glucose in patients with advanced chronic obstructive pulmonary disease. *Clin Physiol* 1995; 15: 319–329.
96. Jakobsson P, Jorfeldt L. Oxygen supplementation increases glucose tolerance during euglycaemic hyperinsulinaemic glucose clamp procedure in patients with severe COPD and chronic hypoxaemia. *Clin Physiol Funct Imaging* 2006; 26: 271–274.
97. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; 364: 829–841.
98. Yeh F, Dixon AE, Marion S, *et al.* Obesity in adults is associated with reduced lung function in metabolic syndrome and diabetes: the Strong Heart Study. *Diabetes Care* 2011; 34: 2306–2313.
99. Lessard A, Alm  ras N, Turcotte H, *et al.* Adiposity and pulmonary function: relationship with body fat distribution and systemic inflammation. *Clin Invest Med* 2011; 34: E64–E70.

100. Mori H, Okubo M, Okamura M, *et al.* Abnormalities of pulmonary function in patients with non-insulin-dependent diabetes mellitus. *Intern Med* 1992; 31: 189–193.
101. Weynand B, Jonckheere A, Frans A, *et al.* Diabetes mellitus induces a thickening of the pulmonary basal lamina. *Respiration* 1999; 66: 12–13.
102. Loukides S, Polyzogopoulos D. The effect of diabetes mellitus on the outcome of patients with chronic obstructive pulmonary disease exacerbated due to respiratory infections. *Respiration* 1996; 63: 170–173.
103. Baker EH, Janaway CH, Philips BJ, *et al.* Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 2006; 61: 284–289.
104. Chakrabarti B, Angus RM, Agarwal S, *et al.* Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD. *Thorax* 2009; 64: 857–862.
105. Archer JRH, Baker EH. Diabetes and metabolic dysfunction in COPD. *Respiratory Medicine: COPD Update* 2009; 5: 67–74.
106. Cazzola M, Calzetta L, Rogliani P, *et al.* High glucose enhances responsiveness of human airways smooth muscle via the Rho/ROCK pathway. *Am J Respir Cell Mol Biol* 2012; 47: 509–516.
107. Seymour JM, Spruit MA, Hopkinson NS, *et al.* The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J* 2010; 36: 81–88.
108. Hopkinson NS, Tennant RC, Dayer MJ, *et al.* A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. *Respir Res* 2007; 8: 25–32.
109. Swallow EB, Reyes D, Hopkinson NS, *et al.* Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007; 62: 115–120.
110. Decramer M, Gosselink R, Troosters T, *et al.* Muscle weakness is related to utilization of health care resources in COPD patients. *Eur Respir J* 1997; 10: 417–423.
111. Garcia-Aymerich J, Félez MA, Escarabill J, *et al.* Physical activity and its determinants in severe chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2004; 36: 1667–1673.
112. Park SW, Goodpaster BH, Strotmeyer ES, *et al.* Decreased muscle strength and quality in older adults with type 2 diabetes: the Health, Aging, and Body Composition Study. *Diabetes* 2006; 55: 1813–1818.
113. Park SW, Goodpaster BH, Strotmeyer ES, *et al.* Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the Health, Aging, and Body Composition study. *Diabetes Care* 2007; 30: 1507–1512.
114. Gregg EW, Beckles GL, Williamson DF, *et al.* Diabetes and physical disability among U.S. adults. *Diabetes Care* 2000; 23: 1272–1277.
115. Miller DK, Lui LY, Perry HM 3rd, *et al.* Reported and measured physical functioning in older inner-city diabetic African Americans. *J Gerontol A Biol Sci Med Sci* 1999; 54: M230–M236.
116. Boirie Y, Short KR, Ahlman B, *et al.* Tissue-specific regulation of mitochondrial and cytoplasmic protein synthesis rates by insulin. *Diabetes* 2001; 50: 2652–2658.
117. Siew ED, Pupim LB, Majchrzak KM, *et al.* Insulin resistance is associated with skeletal muscle protein breakdown in non-diabetic chronic hemodialysis patients. *Kidney Int* 2007; 71: 146–152.
118. Bierbrauer J, Weber-Carstens S. [Insulin resistance and protein catabolism in critically ill patients.] *Anesthesiol Intensivmed Notfallmed Schmerzther* 2011; 46: 268–274.
119. Stump CS, Short KR, Bigelow ML, *et al.* Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. *Proc Natl Acad Sci USA* 2003; 100: 7996–8001.
120. Kelley DE, He J, Menshikova EV, *et al.* Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes* 2002; 51: 2944–2950.
121. Schnell K, Weiss CO, Lee T, *et al.* The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999–2008. *BMC Pulm Med* 2012; 12: 26.
122. Graat-Verboom L, Smeenk FW, van den Borne BE, *et al.* Progression of osteoporosis in patients with COPD: a 3-year follow up study. *Respir Med* 2012; 106: 861–870.
123. McFarlane SI. Bone metabolism and the cardiometabolic syndrome: pathophysiologic insights. *J Cardiometa Syndr* 2006; 1: 53–57.
124. Romme EA, Rutten EP, Smeenk FW, *et al.* Vitamin D status is associated with bone mineral density and functional exercise capacity in patients with chronic obstructive pulmonary disease. *Ann Med* 2012; [Epub ahead of print DOI: 10.3109/07853890.2012.671536].
125. Boucher BJ. Is vitamin D status relevant to metabolic syndrome? *Dermatoendocrinol* 2012; 4: 212–224.
126. Rodríguez-Roisin R, Soriano JB. Chronic obstructive pulmonary disease with lung cancer and/or cardiovascular disease. *Proc Am Thorac Soc* 2008; 5: 842–847.
127. Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. *Eur Respir J* 2010; 35: 913–922.
128. Viscogliosi G, Andreozzi P, Chiriack IM, *et al.* Depressive symptoms in older people with metabolic syndrome: is there a relationship with inflammation? *Int J Geriatr Psychiatry* 2012; [Epub ahead of print; DOI: 10.1002/gps.3817].
129. Sepanjinia K, Modabbernia A, Ashrafi M, *et al.* Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. *Neuropsychopharmacology* 2012; 37: 2093–2100.

130. Katsumata Y, Todoriki H, Higashiuesato Y, *et al*. Metabolic syndrome and cognitive decline among the oldest old in Okinawa: in search of a mechanism. The KCOA Project. *J Gerontol A Biol Sci Med Sci* 2012; 67: 126–134.
131. Reijmer YD, van den Berg E, Dekker JM, *et al*. The metabolic syndrome, atherosclerosis and cognitive functioning in a non-demented population: the Hoorn Study. *Atherosclerosis* 2011; 219: 839–845.
132. McEvoy LK, Laughlin GA, Barrett-Connor E, *et al*. Metabolic syndrome and 16-year cognitive decline in community-dwelling older adults. *Ann Epidemiol* 2012; 22: 310–317.
133. US Department of Health and Human Services. Agency for Healthcare Research and quality. National Quality Measures Clearinghouse. Guideline Synthesis: Chronic Obstructive Pulmonary Disease (COPD): Pulmonary Rehabilitation. Last updated December 2011. www.qualitymeasures.ahrq.gov/syntheses/synthesis.aspx?id=35091 Date last updated: December 2011 Date last accessed: January 9, 2013.
134. Healy GN, Matthews CE, Dunstan DW, *et al*. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–06. *Eur Heart J* 2011; 32: 590–597.
135. Hwang CL, Wu YT, Chou CH. Effect of aerobic interval training on exercise capacity and metabolic risk factors in people with cardiometabolic disorders. *J Cardiopulm Rehabil Prev* 2011; 31: 378–385.
136. Schjerve IE, Tyldum GA, Tjønnå AE, *et al*. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. *Clin Sci (Lond)* 2008; 115: 283–293.
137. Tjønnå AE, Lee SJ, Rognum O, *et al*. Aerobic interval training *versus* continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* 2008; 118: 346–354.
138. Bweir S, Al-Jarrah M, Almalaty AM, *et al*. Resistance exercise training lowers HbA_{1c} more than aerobic training in adults with type 2 diabetes. *Diabetol Metab Syndr* 2009; 1: 27.
139. Tambalis K, Panagiotakos DB, Kavouras SA, *et al*. Responses of blood lipids to aerobic, resistance, and combined aerobic with resistance exercise training: a systematic review of current evidence. *Angiology* 2009; 60: 614–632.
140. Pitsavos C, Panagiotakos DB, Tambalis KD, *et al*. Resistance exercise plus to aerobic activities is associated with better lipids' profile among healthy individuals: the ATTICA study. *QJM* 2009; 102: 609–616.
141. Athyros VG, Tziomalos K, Karagiannis A, *et al*. Cardiovascular benefits of bariatric surgery in morbidly obese patients. *Obes Rev* 2011; 12: 515–512.
142. Landbo C, Prescott E, Lange P, *et al*. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856–1861.
143. Minehira K, Tappy L. Dietary and lifestyle interventions in the management of the metabolic syndrome: present status and future perspective. *Eur J Clin Nut* 2002; 56: 1264–1269.
144. Visioli F. Nutritional support in the pharmacological treatment of metabolic syndrome. *Eur J Pharmacol* 2011; 668: Suppl. 1, S43–S49.
145. Pour OR, Dagogo-Jack S. Prediabetes as a therapeutic target. *Clin Chem* 2011; 57: 215–220.
146. Ajjan RA, Grant PJ. Cardiovascular disease prevention in patients with type 2 diabetes: The role of oral anti-diabetic agents. *Diab Vasc Dis Res* 2006; 3: 147–158.
147. Bailey CJ. Metformin: effects on micro and macrovascular complications in type 2 diabetes mellitus. *Cardiovasc Drugs Ther* 2008; 22: 215–224.
148. Lardizabal JA, Deedwania PC. The role of renin-angiotensin agents in altering the natural history of type 2 diabetes mellitus. *Curr Cardiol Rep* 2010; 12: 464–471.
149. Putnam K, Shoemaker R, Yiannikouris F, *et al*. The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. *Am J Physiol Heart Circ Physiol* 2012; 302: H1219–H1230.
150. Perk J, De Backer G, Gohlke H, *et al*. The fifth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; 33: 1635–1701.
151. Mills EJ, Wu P, Chong G, *et al*. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM* 2011; 104: 109–124.

Chapter 10

Obstructive sleep apnoea and COPD



Walter T. McNicholas and Ruth Lee

SUMMARY: COPD and obstructive sleep apnoea syndrome (OSAS) represent two of the most prevalent chronic respiratory disorders, and cardiovascular diseases are major comorbidities in both. Coexistence of both disorders (known as “overlap syndrome”) has been estimated to occur in 1% of the general adult population, and overlap syndrome patients have worse nocturnal hypoxaemia and hypercapnia than COPD and OSAS patients alone. The severity of obstructive ventilatory impairment and hyperinflation, especially the inspiratory capacity (IC) to total lung capacity (TLC) ratio, correlates with the severity of sleep-related breathing disturbances. Early treatment with continuous positive airway pressure (CPAP) improves survival, reduces hospitalisation and pulmonary hypertension, and also reduces hypoxaemia. Evidence of systemic inflammation and oxidative stress in COPD and sleep apnoea provides insight into potential interactions between both disorders, which may predispose to cardiovascular disease. Long-term outcome studies of overlap patients currently underway should provide further evidence of the clinical significance of overlap syndrome. Studies of overlap syndrome patients at a clinical, physiological and molecular level should provide insight into disease mechanisms and consequences of COPD and OSAS, in addition to identifying potential relationships with cardiovascular disease.

KEYWORDS: Cardiovascular disease, COPD, hypoxia, obstructive sleep apnoea, systemic inflammation

Pulmonary and Sleep Disorders Unit, St Vincent's University Hospital, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland.

Correspondence: W.T. McNicholas, Pulmonary and Sleep Disorders Unit, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland.
Email: walter.mcnicholas@ucd.ie

Eur Respir Monogr 2013; 59: 135–143.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10012012
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Sleep has several effects on breathing, including changes in central respiratory control, lung mechanics and muscle contractility. These effects do not have an adverse impact on healthy individuals but may result in significant hypoxaemia and hypercapnia in patients with COPD, particularly during rapid eye movement (REM) sleep [1]. Gas exchange in sleeping normal subjects is largely a consequence of hypoventilation, although ventilation/perfusion abnormalities may also contribute. In COPD patients, hypoventilation is more pronounced, particularly during REM sleep, due to a number of factors: airflow obstruction, hyperinflation, respiratory muscle dysfunction, blunted ventilatory responses to hypercapnia and/or hypoxia, ventilation/perfusion mismatching, and medications such as loop diuretics and oral steroids. Sleep disturbance is also common in COPD [2, 3] and it is likely that it is a consequence of the underlying lung disease,

although adverse effects of drug therapy on sleep quality may also contribute. It is likely that sleep disturbance contributes to the nonspecific daytime symptoms of chronic fatigue and lethargy, and to the overall impairment in quality of life described by these patients [4]. While the relationships between sleep and COPD are separate and distinct from sleep apnoea, there are interactions of sleep and breathing that may influence the relationship between obstructive sleep apnoea syndrome (OSAS) and COPD. In particular, patients with both COPD and OSAS develop more pronounced nocturnal oxygen desaturation than COPD or OSAS alone, which predisposes to pulmonary hypertension and more severe cardiovascular disease [5].

In this chapter, we discuss the clinical syndrome in which COPD and OSAS coexist, commonly referred to as “overlap syndrome”. The chapter also reviews the epidemiology, pathophysiology, cardiovascular comorbidity and management of this prevalent disorder.

The epidemiology of overlap syndrome

The prevalence of sleep-disordered breathing (SDB) in COPD patients and of COPD in OSAS patients approximates the prevalence of each disorder in the general population [6]. However, as COPD and OSAS represent two of the most prevalent chronic respiratory disorders in clinical practice, overlap syndrome is likely to have a relatively high prevalence on this basis alone. Data from the Third National Health and Nutrition Examination Survey (NHANES III), which involved 9,838 normal subjects, indicated a prevalence of 16.8% for the combination of a forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio of <70% and a FEV₁ of >80% predicted, and 7.7% for a FEV₁/FVC ratio <70% where FEV₁ was between 50–80% pred [7]. In the Wisconsin Cohort study of 602 middle-aged working adults [8], an apnoea/hypopnoea index (AHI) of ≥5 events per hour was found in 24% of males and 9% of females, although these figures fell to 4% of males and 2% of females when an AHI of ≥5 events per hour was combined with daytime sleepiness, which represent the minimum criteria for the clinical syndrome of OSAS [9].

A recent comprehensive review indicated that the two disorders are likely to coexist in approximately 1% of adult males in the general population, but the coexistence of asymptomatic lower airway obstruction with SDB is considerably higher, as might be expected from the epidemiology of the individual disorders [6]. In the World Health Organization (WHO)-sponsored MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) II project, OSAS prevalence in COPD was relatively high at 11.3%, but lower airway obstruction did not predispose to OSAS, nor did OSAS to lower airway obstruction [10]. Overlap syndrome occurred in 1% of subjects, but AHI ≥5 events per hour alone with FEV₁/FVC <70% occurred in 3%. LÓPEZ-ACEVEDO *et al.* [11] found COPD in 10–20% of patients with OSAS. Overall, these data indicate that the prevalence of sleep apnoea in COPD patients approximates its prevalence in the general population, and *vice versa*.

Several confounding factors may influence the relationship between COPD and OSAS, particularly body mass index (BMI) and smoking. Obesity is a key factor in OSAS [12], yet low BMI is common in COPD, especially in patients with advanced disease, which should reduce the likelihood of OSAS. Smoking is a risk factor for both COPD and OSAS, and several reports found higher AHI in smokers than nonsmokers. A report based on the Wisconsin cohort found that AHI ≥5 events per hour was three times more likely in current smokers than never-smokers [13]. OSAS and COPD are also more common in the elderly, and CHAOUAT *et al.* [5] reported that overlap patients in their sleep clinic cohort were older than patients with OSAS alone.

Pathophysiology of sleep-related disturbances in overlap syndrome

Sleep quality is impaired in COPD and there is diminished REM sleep, which protects against sleep apnoea because it is more pronounced in OSAS during REM [14]. The principal basis for disturbances in ventilation and gas exchange during sleep in COPD, independent of sleep apnoea, relates to

augmented physiological adaptations that are normally associated with sleep [1]. Respiratory muscle responses to respiratory centre outputs are diminished, particularly during REM sleep and especially those involving the accessory muscles of respiration; this is particularly relevant in COPD where lung hyperinflation may reduce diaphragmatic efficiency, thus necessitating an increased accessory muscle contribution to breathing [15]. Minute ventilation falls during non-REM and more so during REM sleep, even in normal subjects; this is predominantly because of a reduction in tidal volume due to increased upper airway resistance and diminished inspiratory drive, with a slight fall in arterial oxygen saturation (S_{a,O_2}) that is not clinically significant in normal subjects [16]. However, in COPD, this reduction in ventilation is augmented, resulting in greater hypoxaemia during sleep with associated hypercapnia [17]. As many such patients have hypoxaemia while awake, they are especially prone to nocturnal oxygen desaturation as they are on the steep portion of the oxyhaemoglobin dissociation curve. A recent report also indicated that upper airway narrowing without the presence of obstructive apnoea or hypopnoea is significantly related to nocturnal oxygen desaturation in COPD patients [18].

Several pathophysiological factors influence the relationship between COPD and OSAS (table 1). COPD-related factors that may predispose to SDB include rostral shift of peripheral oedema when supine, resulting in fluid accumulation in the neck, and thus contributing to pharyngeal narrowing [19]. While there are no data in COPD, this phenomenon might be particularly expected in patients with cor pulmonale where peripheral oedema is a major feature. BMI and cigarette smoking also affect pathophysiological relationships. Neck obesity contributes to upper airway narrowing, which is key to the pathophysiology of OSAS [20]. Truncal obesity promotes ventilatory disturbances by reducing chest wall compliance and respiratory muscle strength [21]. Furthermore, truncal obesity is associated with reduced functional residual capacity, which contributes to ventilation/perfusion mismatching. However, many patients with advanced COPD have a low BMI, which protects against upper airway obstruction. Cigarette smoking predisposes to upper airway obstruction by increasing upper airway resistance due to local inflammation and oedema [20].

The medication used in COPD may also influence the interaction between COPD and OSAS. Theophyllines [22], inhaled anti-cholinergic agents [23] and inhaled long-acting β -agonists [24] ameliorate nocturnal oxygen desaturation, perhaps due to reductions in both gas trapping and lower airway obstruction. Corticosteroids may predispose to upper airway obstruction by promoting central obesity and fluid retention with associated upper airway narrowing, in addition to myopathy and metabolic alkalosis. In contrast, theophylline therapy has been demonstrated to reduce AHI in patients with OSAS without COPD [25].

Gas exchange and pulmonary function in overlap syndrome

Overlap syndrome patients have a greater degree of hypoxaemia and hypercapnia than COPD patients matched for Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. They also have more severe pulmonary hypertension and right heart failure, and suffer higher morbidity [5, 26]. The principal mechanism of increased pulmonary hypertension is likely to be the greater degree of hypoxaemia in overlap syndrome patients [27]. LÓPEZ-ACEVEDO *et al.* [11] reviewed 73 patients with overlap syndrome and found that daytime hypercapnia correlated with more severe SDB and worse nocturnal hypoxaemia, and the severity of obstructive ventilatory impairment was associated with worse SDB, especially during REM sleep.

Table 1. Pathophysiological interactions between COPD, sleep and obstructive sleep apnoea syndrome (OSAS)

Direct effects of COPD on sleep
Diminished sleep quality
Oxygen desaturation
Promoting factors for OSAS in COPD
Rostral fluid shift when supine
Cigarette smoking
Medication <i>e.g.</i> corticosteroids
Protective factors against OSAS in COPD
Low BMI
Diminished REM sleep
Medication <i>e.g.</i> theophylline

BMI: body mass index; REM: rapid eye movement.

The impact of COPD on sleep quality

While sleep disturbance is expected in patients with overlap syndrome because of the impact of OSAS, there is also evidence that COPD alone can disturb sleep [2]. However, data on the mechanisms of this sleep disturbance are limited. In a group of 30 patients with overlap syndrome, KWON *et al.* [28] found significant associations between sleep efficiency and lung hyperinflation after adjusting for potential confounders such as age, sex, BMI, AHI, FEV₁ % pred, oxygen saturation nadir, medication and cardiac disease. The precise mechanisms underlying the findings were unclear but nonetheless, the results suggested that therapies aimed at reducing lung hyperinflation may improve sleep efficiency in patients with overlap syndrome. A recent report from our department confirmed previous findings of poor sleep quality in patients with COPD without coexisting sleep apnoea, and found that awake levels of arterial oxygen tension (P_{a,O_2}) represented the best predictor of nocturnal sleep efficiency [14].

Overlap syndrome and cardiovascular disease

A major comorbidity of both COPD and OSAS is cardiovascular disease [29, 30], and systemic inflammation may be an important shared mechanism [31, 32]. Intermediate factors are also important as smoking [33] and obesity [34] are associated with increased systemic inflammatory markers, such as interleukin (IL)-6, tumour necrosis factor (TNF)- α and reactive oxygen species. The relationship between COPD and cardiovascular disease is covered in-depth in another chapter of this issue of the *European Respiratory Monograph* (ERM) [35].

In OSAS, the major health burden is the significantly increased risk of cardiovascular disease [36]. Large-scale epidemiological studies have demonstrated an independent relationship between OSAS and cardiovascular disorders, particularly systemic hypertension [37, 38] but also ischaemic heart disease [39], congestive cardiac failure [40] and stroke [36, 41]. Data from the Wisconsin Cohort Study demonstrated that the presence of moderate-to-severe OSAS as indicated by an AHI >15 events per hour is associated with a relative risk of 2.89 of developing hypertension over 8 years, following adjustment for potential confounders [38]. The prevalence of hypertension in OSAS populations is over 50%, and OSAS is cited as the first differential in treatable causes of hypertension [42]. The prevalence of OSAS is particularly high in patients with drug-resistant hypertension; a recent study found occult OSAS in up to 83% of patients who had uncontrolled hypertension despite taking three or more antihypertensive agents at optimum doses [43]. Hypertension in OSAS patients is frequently nocturnal and potentially driven by concomitant SDB.

Patients with severe OSAS are significantly more likely to die of cardiovascular causes than those without OSAS [44], and while the absolute risk increase attributable to SDB may be relatively small at an individual level, its high prevalence makes it an important contributor to cardiovascular morbidity and mortality at a population level. Several reports have indicated that OSAS may also contribute to coronary atherogenesis [45] and to worse outcomes in subjects with established coronary artery disease (CAD) [46]. Furthermore, studies utilising carotid ultrasonography have shown severe OSAS to be associated with increased carotid intima medial thickness [47], which is a recognised marker of atherosclerosis.

Mechanisms of cardiovascular disease in COPD, OSAS and overlap syndrome

The mechanisms of cardiovascular disease in COPD patients are covered in-depth in another chapter of this issue of the ERM [35]. However, to provide a brief summary, mechanisms of cardiovascular disease in COPD include hypoxia, systemic inflammation and oxidative stress, which promote endothelial dysfunction and atherosclerosis, in addition to sympathetic nervous

system overactivity and vascular dysfunction. COPD also increases elastolytic activity and accentuates connective tissue degradation, the latter resulting in arterial stiffening [48].

In OSAS, mechanisms of cardiovascular disease include increased sympathetic nervous system activity [49], systemic inflammation [32, 50], oxidative stress [51], endothelial dysfunction [52] and metabolic dysregulation, with the latter involving insulin resistance and disordered lipid metabolism [36, 53]. The mechanisms of OSAS are summarised in figure 1. Intermittent hypoxia is a key feature in systemic inflammation and oxidative stress in OSAS because of the associated intermittent re-oxygenation [51], which has been compared with reperfusion injury, and activates the inflammatory transcription factor nuclear factor (NF)- κ B with increased production of related cytokines, including TNF- α and IL-8 [54]. Inflammation plays a key role in atherosclerotic plaque formation, from initiation of the fatty streak to the later stages of plaque rupture [55]. Endothelial dysfunction develops at an early stage in response to oxidised lipids, inflammatory cytokines, such as TNF- α , IL-1 and IL-6, and other factors, including reactive oxygen species. This process leads to upregulation of intercellular adhesion molecules, which promote rolling and adherence of leukocytes to the endothelium. Monocytes and T-cells penetrate the vascular wall where monocytes transform into macrophages, which ingest oxidised lipids to form foam cells. These cells accumulate to form a lipid pool, which is a central component of the early atherosclerotic plaque. Both COPD and OSAS are associated with increased activation of many inflammatory cell and molecular mechanisms associated with atherosclerosis [36, 48].

Hypoxia plays an important role in the progression of atherosclerosis by stimulating angiogenesis within the atherosclerotic plaque [56], principally *via* activation of the adaptive hypoxia responsive transcription factor, hypoxia inducible factor (HIF)-1. Furthermore, important interactions occur between lipids and hypoxia in the development of atherosclerosis [57]. These findings suggest that greater hypoxaemia in overlap syndrome might be more likely predispose to atherosclerosis than in COPD or OSAS alone; this, however, is unproven. Hypercapnia also modulates inflammatory responses in a variety of settings, including sepsis and ischaemia-reperfusion, and there is evidence of an anti-inflammatory effect in both *in vitro* and *in vivo* models [58]. These findings underline the complexity of potential interactions between hypoxia and hypercapnia in the inflammatory response.

While systemic inflammation and cardiovascular disease develop in both COPD and OSAS, there is limited evidence of the possible interactions between the disorders in these developments. Nocturnal oxygen desaturation is greater in patients with overlap syndrome than in those with COPD or OSAS alone [5], and apnoea-associated desaturation is more pronounced. Daytime hypercapnia is also more common in overlap patients [59]. This more pronounced hypoxaemia and hypercapnia might result in greater cardiovascular

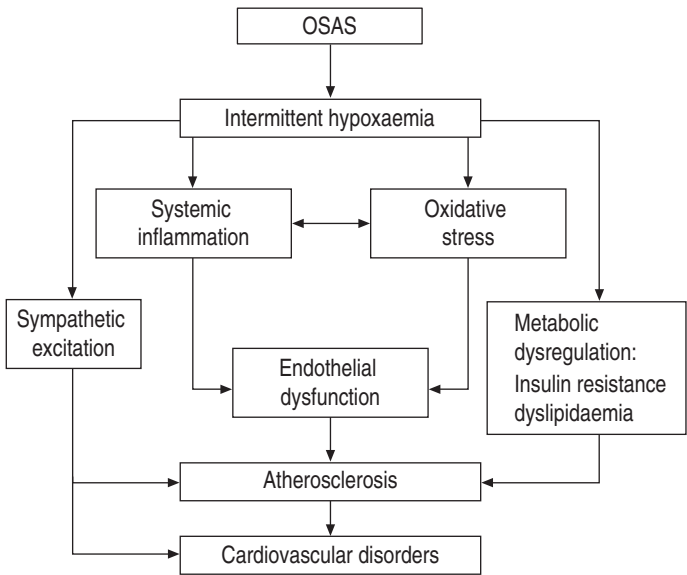


Figure 1. Mechanisms associated with intermittent hypoxia in obstructive sleep apnoea syndrome (OSAS) contributing to cardiovascular diseases. The intermittent hypoxia and sleep fragmentation associated with OSAS result in a variety of responses, including increased sympathetic nervous system activity, systemic inflammation, oxidative stress and metabolic dysregulation, the latter involving insulin resistance and disordered lipid metabolism. Inflammation and oxidative stress produce endothelial dysfunction, and the various mechanisms combine to promote the development of atherosclerosis and cardiovascular disease.

morbidity and mortality, and there is some limited evidence to support this possibility [5, 60]. To date, no study has investigated the possible basic interactions between COPD and OSAS, although systemic inflammation does develop in both disorders and systemic hypoxaemia is more pronounced in overlap syndrome than in each disorder alone. However, a recent report by SHIINA *et al.* [61] involving 524 males with OSAS indicated that overlap patients demonstrated greater arterial stiffness, as measured by brachial–ankle pulse wave velocity, than patients with OSAS alone. Thus, it seems likely that overlap syndrome is associated with greater cardiovascular morbidity and mortality than each disorder alone; further studies are required to confirm this. Basic interactions between COPD and OSAS that may contribute to the development of cardiovascular disease are summarised in figure 2.

Management considerations in overlap syndrome

The first management principle of sleep-related breathing disturbances in COPD should be to optimise the underlying condition, which will almost invariably benefit breathing while asleep. There is evidence that bronchodilator therapy ameliorates nocturnal oxygen desaturation in COPD [22–24] without significantly affecting sleep quality. However, coexisting OSAS adds a further dimension and some form of nocturnal positive airway pressure therapy plays a key role in the management of patients with overlap syndrome. Where the predominant nocturnal abnormality relates to OSAS, continuous positive airway pressure (CPAP) is likely to be the preferred option. However, if there is evidence of coexisting hypoventilation with sustained nocturnal oxygen desaturation and/or hypercapnia, bi-level positive airway pressure therapy may be more appropriate.

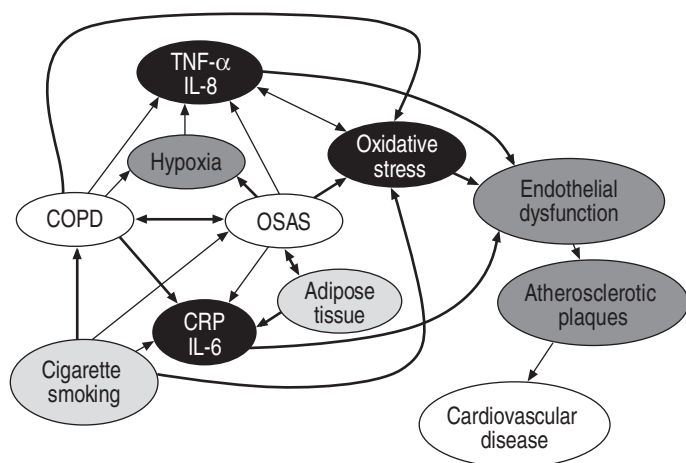


Figure 2. Overlapping molecular mechanisms of systemic inflammation in COPD and obstructive sleep apnoea syndrome (OSAS). The overlapping molecular pathways of systemic inflammation in COPD and OSAS identify areas in which an evidence base exists for inflammatory pathways common to each disorder (the thickness of the arrows is representative of the weight of evidence in favour). Both COPD and OSAS are associated with elevated levels of C-reactive protein (CRP) and interleukin (IL)-6, in addition to tumour necrosis factor (TNF)- α and IL-8, and are also associated with oxidative stress. However, cigarette smoking and obesity are confounding variables in these associations. Hypoxia is a key factor in elevated TNF- α production in OSAS, which is particularly relevant to overlap syndrome. Each inflammatory pathway has been associated with atherogenesis and subsequent cardiovascular disease. Reproduced and modified from [6] with permission from the publisher.

Data from TORALDO *et al.* [62] support early treatment with nasal CPAP in overlap patients. In their cohort of patients with both severe OSAS and mild-to-moderate COPD, arterial blood gases and mean pulmonary artery pressure improved and stabilised after 3 months of CPAP therapy, with the greatest improvements being in Epworth Sleepiness Score and a percentage of total recording time spent with oxygen saturation of less than 90% (CT90), in addition to maximal inspiratory force. Improvement in these parameters remained stable over 12 months' follow-up.

Outcomes in overlap syndrome

Pulmonary hypertension is more prevalent in overlap syndrome patients [5] and recent studies indicate that these patients have a higher mortality than those with COPD alone. MARIN *et al.* [60] assessed the relationship of overlap

syndrome to mortality and first-time hospitalisation due to COPD exacerbation, and also examined the impact of CPAP therapy on these major outcomes. The authors reported that patients with overlap syndrome who were not treated with CPAP had a significantly higher mortality rate (relative risk 1.79) and were also more likely to suffer a severe COPD exacerbation leading to hospitalisation (relative risk 1.70) compared with the patient group with COPD alone. The authors concluded that CPAP therapy in overlap syndrome patients is associated with improved survival and decreased hospitalisation rate.

MACHADO *et al.* [63] evaluated the impact of OSAS treatment with CPAP on the survival of hypoxaemic COPD patients and reported that CPAP therapy was associated with higher survival in patients with both moderate-to-severe OSAS and hypoxaemic COPD. Of the 603 hypoxaemic COPD patients receiving long-term oxygen therapy, 95 were diagnosed with moderate-to-severe OSAS. Of this OSAS group, 61 (64%) patients accepted and were adherent to CPAP treatment, and 34 (36%) did not accept or were not adherent and were considered “not treated”. The 5-year survival rate was significantly higher in the CPAP-treated group (71%) compared with the non-treated group (26%). After adjusting for several potential confounding factors, patients treated with CPAP continued to have a significantly lower risk of death.

Conclusions and future research directions in overlap syndrome

Overlap syndrome is highly prevalent but frequently unrecognised because of the failure to consider possible coexisting SDB among individual patients with COPD in clinical practice. Overlap syndrome is associated with greater hypoxaemia and hypercapnia than COPD or OSAS alone, which may have significant cardiovascular implications. Early recognition and appropriate therapy with CPAP will reduce morbidity and mortality. Despite the high prevalence of overlap syndrome, only limited data are available on its pathophysiological and clinical consequences. Long-term follow-up studies are lacking on the pathophysiological and clinical consequences of overlap syndrome, although some clinical outcome studies in this area have commenced [64, 65].

The magnitude and consequences of inflammation, oxidative stress and leukocyte dysfunction in the overlapping mechanisms of overlap syndrome should be better defined in future studies. The role of inflammatory markers in the prediction of cardiovascular morbidity in COPD and OSAS is lacking, particularly in patients with overlap syndrome. Studies in overlap patients are likely to provide insight regarding the nature and significance of these responses.

Statement of Interest

None declared.

References

1. McNicholas WT. Impact of sleep in COPD. *Chest* 2000; 117: Suppl. 2, 48S–53S.
2. Valipour A, Lavie P, Lothaller H, *et al.* Sleep profile and symptoms of sleep disorders in patients with stable mild to moderate chronic obstructive pulmonary disease. *Sleep Medicine* 2011; 12: 367–372.
3. Cormick W, Olson L, Hensley M, *et al.* Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. *Thorax* 1986; 41: 846–854.
4. Breslin E, van der Schans C, Breukink S, *et al.* Perception of fatigue and quality of life in patients with COPD. *Chest* 1998; 114: 958–964.
5. Chaouat A, Weitzenbum E, Krieger J, *et al.* Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *Am J Respir Crit Care Med* 1995; 151: 82–86.
6. McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. *Am J Respir Crit Care Med* 2009; 180: 692–700.
7. Celli B, Halbert R, Isonaka S, *et al.* Population impact of different definitions of airway obstruction. *Eur Respir J* 2003; 22: 268–273.
8. Young T, Palta M, Dempsey J, *et al.* The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230–1235.

9. Flemons WW, Buysse D, Redline S, *et al.* Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; 22: 667–689.
10. Bednarek M, Plywaczewski R, Jonczak L, *et al.* There is no relationship between chronic obstructive pulmonary disease and obstructive sleep apnea syndrome: a population study. *Respiration* 2005; 72: 142–149.
11. López-Acevedo M, Torres-Palacios A, Elena Ocasio-Tascón M, *et al.* Overlap syndrome: an indication for sleep studies? *Sleep Breath* 2009; 13: 409–413.
12. McNicholas WT. Diagnosis of obstructive sleep apnea in adults. *Proc Am Thorac Soc* 2008; 5: 154–160.
13. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002; 165: 1217–1239.
14. McSharry DG, Ryan S, Calverley P, *et al.* Sleep quality in chronic obstructive pulmonary disease. *Respirology* 2012; 17: 1119–1124.
15. Johnson M, Remmers J. Accessory muscle activity during sleep in chronic obstructive pulmonary disease. *J Appl Physiol* 1984; 57: 1011–1017.
16. Douglas N, White D, Pickett C, *et al.* Respiration during sleep in normal man. *Thorax* 1982; 37: 840–844.
17. Mulloy E, McNicholas WT. Ventilation and gas exchange during sleep and exercise in severe COPD. *Chest* 1996; 109: 387–394.
18. Corda L, Novali M, Montemurro LT, *et al.* Predictors of nocturnal oxyhemoglobin desaturation in COPD. *Respir Physiol Neurobiol* 2011; 179: 192–197.
19. Redolfi S, Yumino D, Ruttanaumpawan P, *et al.* Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men. *Am J Respir Crit Care Med* 2009; 179: 241–246.
20. Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. *Eur Respir J* 1995; 8: 1161–1178.
21. Poulain M, Doucet M, Major GC, *et al.* The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. *Can Med Assoc J* 2006; 174: 1293–1299.
22. Mulloy E, McNicholas WT. Theophylline improves gas exchange during rest, exercise, and sleep in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993; 148: 1030–1036.
23. McNicholas WT, Calverley PMA, Lee A, *et al.* Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. *Eur Respir J* 2004; 23: 825–831.
24. Ryan S, Doherty LS, Rock C, *et al.* Effects of salmeterol on sleeping oxygen saturation in chronic obstructive pulmonary disease. *Respiration* 2010; 79: 475–481.
25. Mulloy E, McNicholas WT. Theophylline in obstructive sleep apnea. A double-blind evaluation. *Chest* 1992; 101: 753–757.
26. Shteinberg M, Weiler-Ravel D, Adir Y. The overlap syndrome: obstructive sleep apnea and chronic obstructive pulmonary disease. *Harefuah* 2009; 148: 333–336.
27. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32: 1371–1385.
28. Kwon JS, Wolfe LF, Lu BS, *et al.* Hyperinflation is associated with lower sleep efficiency in COPD with co-existent obstructive sleep apnea. *COPD* 2009; 6: 441–445.
29. Somers VK, White DP, Amin R, *et al.* Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing in collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008; 118: 1080–1111.
30. Sin DD, Man SFP. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005; 2: 8–11.
31. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; 107: 1514–1519.
32. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? *Thorax* 2009; 64: 631–636.
33. Yanbaeva DG, Dentener MA, Creutzberg EC, *et al.* Systemic effects of smoking. *Chest* 2007; 131: 1557–1566.
34. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2004; 92: 347–355.
35. MacLay JD, MacNee W. Assessment of cardiovascular comorbidity. *Eur Respir Monogr* 2013; 59: 28–49.
36. McNicholas WT, Bonsignore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* 2007; 29: 156–178.
37. Nieto FJ, Young TB, Lind BK, *et al.* Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000; 283: 1829–1836.
38. Peppard PE, Young T, Palta M, *et al.* Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; 342: 1378–1384.
39. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. *Eur Respir J* 2006; 28: 596–602.
40. Gottlieb DJ, Yenokyan G, Newman AB, *et al.* Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure. *Circulation* 2010; 122: 352–360.

41. Redline S, Yenokyan G, Gottlieb DJ, *et al.* Obstructive sleep apnea hypopnea and incident stroke. *Am J Respir Crit Care Med* 2010; 182: 269–277.
42. Chobanian AV, Bakris GL, Black HR, *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206–1252.
43. Logan AG, Perlikowski SM, Mente A, *et al.* High prevalence of unrecognized sleep apnea in drug-resistant hypertension. *J Hypertens* 2001; 19: 2271–2277.
44. Punjabi NM, Caffo BS, Goodwin JL, *et al.* Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009; 6: e1000132.
45. Hayashi M, Fujimoto K, Urushibata K, *et al.* Nocturnal oxygen desaturation correlates with the severity of coronary atherosclerosis in coronary artery disease. *Chest* 2003; 124: 936–941.
46. Peker Y, Hedner J, Kraiczi H, *et al.* Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 2000; 162: 81–86.
47. Drager LF, Bortolotto LA, Lorenzi MC, *et al.* Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 613–618.
48. MacNee W, Maclay J, McAllister D. Cardiovascular injury and repair in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 824–833.
49. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol* 2010; 7: 677–685.
50. Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: Oxidative stress, inflammation, and much more. *Am J Respir Crit Care Med* 2008; 177: 369–375.
51. Lavie L. Obstructive sleep apnoea syndrome – an oxidative stress disorder. *Sleep Med Rev* 2003; 7: 35–51.
52. Berger S, Lavie L. Endothelial progenitor cells in cardiovascular disease and hypoxia–potential implications to obstructive sleep apnea. *Transl Res* 2011; 158: 1–13.
53. Lui MM, Ip MS. Disorders of glucose metabolism in sleep-disordered breathing. *Clin Chest Med* 2010; 31: 271–285.
54. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 2005; 112: 2660–2667.
55. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685–1695.
56. Sluimer JC, Daemen MJ. Novel concepts in atherogenesis: angiogenesis and hypoxia in atherosclerosis. *J Pathol* 2009; 218: 7–29.
57. Savransky V, Nanayakkara A, Li J, *et al.* Chronic intermittent hypoxia induces atherosclerosis. *Am J Respir Crit Care Med* 2007; 175: 1290–1297.
58. Laffey JG, Tanaka M, Engelberts D, *et al.* Therapeutic hypercapnia reduces pulmonary and systemic injury following *in vivo* lung reperfusion. *Am J Respir Crit Care Med* 2000; 162: 2287–2294.
59. Bradley TD, Rutherford R, Lue F, *et al.* Role of diffuse airway obstruction in the hypercapnia of obstructive sleep apnea. *Am Rev Respir Dis* 1986; 134: 920–924.
60. Marin JM, Soriano JB, Carrizo SJ, *et al.* Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010; 182: 325–331.
61. Shiina K, Tomiyama H, Takata Y, *et al.* Overlap syndrome: additive effects of COPD on the cardiovascular damages in patients with OSA. *Respir Med* 2012; 106: 1335–1341.
62. Toraldo D, De Nuccio F, Nicolardi G. Fixed-pressure nCPAP in patients with obstructive sleep apnea (OSA) syndrome and chronic obstructive pulmonary disease (COPD): a 24-month follow-up study. *Sleep Breath* 2010; 14: 115–123.
63. Machado MCL, Vollmer WM, Togeiro SM, *et al.* CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. *Eur Respir J* 2010; 35: 132–137.
64. Soriano JB, Yanez A, Renom F, *et al.* Set-up and pilot of a population cohort for the study of the natural history of COPD and OSA: the PULSAIB study. *Prim Care Respir J* 2010; 19: 140–147.
65. Larsson LG, Lindberg A. Concomitant obstructive sleep apnea and chronic obstructive pulmonary disease: study design – the OLIN OSAS-COPD study. *Clin Respir J* 2008; 2: Suppl. 1, 120–122.

Chapter 11

Management of depression and anxiety in COPD



Paul A. Cafarella, Tanja W. Effing*, Christopher Barton#, David Ahmed*, and Peter Anthony Frith**

SUMMARY: Depression and anxiety are prevalent comorbidities in COPD and often appear together. Numerous theoretical models have been proposed to explain this relationship, with most suggesting bidirectional and complex pathways. Mental health assessment in COPD remains too infrequent and should be integrated into standard practice. Appropriate use of mental health screening tools, diagnostic resources and referral pathways should be implemented for optimal management. There is evidence that depression and anxiety in COPD negatively impacts on important health outcomes, such as COPD symptom burden, physical function, health-related quality of life, adherence with recommended treatments and mortality whilst increasing disability, exacerbation rates, hospitalisations and length of stay. Treatment options for managing depression and anxiety in COPD are less frequently documented. Whilst some evidence exists supporting the efficacy of pulmonary rehabilitation, pharmacological therapy, cognitive behavioural therapy, self-management programmes, relaxation and palliative care interventions in managing depression and anxiety in COPD, there remains a paucity of high-quality studies in the field consequently limiting integration into evidence-based clinical guidelines.

KEYWORDS: Anxiety, comorbidities, COPD, depression, mental health assessment, treatment

*Dept of Respiratory Medicine, Repatriation General Hospital, Daw Park, and

#Social Health Sciences, Flinders University, Bedford Park, Australia.

Correspondence: P.A. Frith, Dept of Respiratory Medicine, Repatriation General Hospital, 216 Daws Road, Daw Park, SA 5041, Australia.
Email: Peter.Frith@health.sa.gov.au

Eur Respir Monogr 2013; 59: 144–163.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10012112
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

The presence of depression and/or anxiety as comorbidities of COPD has been described with increasing frequency over the last 10 years. Whereas the high prevalence of mental health problems in COPD patients and their impact on physical outcomes have been regularly documented [1, 2], less has been published regarding the aetiology, assessment and treatment of mental health problems in COPD populations [3–5]. After summarising epidemiological evidence and aetiological theories, this chapter will provide an overview of what is known about the assessment, impacts and treatments of depression and anxiety in COPD patients, concluding with some recommendations.

Psychological distress has been identified as an important public-health issue associated with chronic diseases in working Australians, with COPD ranking highly as one of the associated conditions [6]. Depression and anxiety are common comorbidities experienced by patients with COPD and often appear together [7]. Different subtypes of depression and anxiety disorders have been defined within the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (table 1) [8].

The two major forms of depression include bipolar and unipolar depression. Patients with bipolar disorders cycle between depressive and manic episodes, while those with unipolar depression never present with mania or hypomania. Unipolar forms of depression will be the focus for discussion as they are considerably more prevalent than bipolar depressive disorders in the community and are most commonly studied in the COPD literature. Symptoms of unipolar depressive disorders are listed in table 1. Depression can range in severity from short-term episodes and mild symptoms through to severe long-term clinical depression.

Studies of anxiety disorders experienced by patients with COPD have focussed on generalised anxiety disorder and panic disorder, while a smaller number of studies have described social phobia amongst patients with COPD. Generalised anxiety disorder is characterised by at least 6 months of persistent and excessive anxiety and worry (table 1). Panic disorder is characterised by recurrent unexpected panic attacks about which there is persistent concern and may occur with or without agoraphobia. Social phobias are characterised by clinically significant anxiety provoked by exposure to certain types of social or performance situations, often leading to avoidance behaviour. Severity of anxiety, as with depression, is determined by both the number and the level of symptoms, as well as the degree of functional impairment [6]. The clinical course of depression and anxiety disorders is acknowledged to be variable and people can move in and out of diagnostic subtypes over time [8].

There is wide variation in estimates of the prevalence of depression in COPD, ranging from 7% to 80% [12, 13]. Meta-analysis has also been used to provide an estimate of depression pooled across studies. In 2000, YOHANNES *et al.* [14] reported a prevalence of depression of 40% (95% CI 36–44%), arising from a meta-analysis based on a total population of 900 subjects drawn from 11 studies. The subjects in the included studies were mostly from outpatient or inpatient settings and provided an indication of the prevalence of depression likely to be found in a respiratory clinic. This is consistent with an estimate for prevalence of depression from a large, nationally representative sample of the US population, which found 40% of 1,736 participants with COPD reported three or more symptoms indicative of depression from the eight-item Center for Epidemiological Studies of Depression (CES-D) questionnaire [15]. Participants with COPD were more likely to report depressive symptoms than people with stroke, hypertension, diabetes, coronary heart disease, arthritis or cancer [15].

Another recent meta-analysis that included 39,587 patients with COPD and 39,431 controls without COPD found a prevalence of depression of 24.6% amongst COPD patients, compared with 11.7% amongst control subjects [16]. This meta-analysis included eight high-quality studies that confirmed COPD by spirometry and assessed depression symptoms using validated questionnaires. Seven of these studies included COPD patients in primary care. These authors also reported that depression is more likely in severe COPD.

Estimates for the prevalence of anxiety are also available from systematic reviews and meta-analysis. One systematic review reported the prevalence of anxiety from 19 studies as ranging from 10% up to 100% [12]. A more recent systematic review that only included studies published between 1999 and 2009 (22 studies) found the prevalence of anxious symptomology ranged from 6% to 74%, and clinical anxiety was found in up to 55% of COPD patients [13]. A meta-analysis published in 2000 [14], which included a total population of 539 patients with COPD drawn from nine studies, estimated prevalence to be 36% (95% CI 31–41%), which is much higher than in the general public [17]. Studies that have used standard diagnostic procedures have found prevalence

Table 1. Categories of mood and anxiety disorders with depression as the dominant symptom[#]

	Characteristics	Major symptoms
Mood disorder		
MDD, the most severe form of depression	One or more major depressive episodes with at least 2 weeks of depressed mood or loss of interest and at least four additional symptoms of depression	Depressed mood Markedly diminished interest or pleasure in almost all activities Significant weight loss or weight gain Sleep disturbance Psychomotor agitation or retardation Fatigue or loss of energy Feelings of worthlessness or excessive or inappropriate guilt Diminished ability to think, concentrate or make decisions Recurrent thoughts of death or suicide
DD, a less severe but chronic form of depression	The presence of depressed mood for at least 2 years for more days than not, accompanied by at least two additional symptoms, but does not meet criteria for major depressive episode	During periods of depressed mood: poor appetite or overeating, sleep disturbance, low energy or fatigue, low self-esteem, poor concentration and feelings of hopelessness
Bipolar I	One or more manic or mixed episodes usually accompanied by major depressive episodes Three or more symptoms during the period of mood disturbance	A distinct period of elevated, expansive or irritable mood with: 1) inflated self-esteem or grandiosity; 2) decreased need for sleep; 3) talkative; 4) racing thoughts; 5) easily distracted; 6) increase in goal-directed activity; and 7) excessive involvement in pleasurable activities that have high potential for painful consequences
Bipolar II	One or more major depressive episode accompanied by at least one hypomanic episode	
Anxiety disorder		
Generalised anxiety disorder	Diagnosed by 6 months of persistent and excessive anxiety and worry	Restlessness or feeling on edge, easily fatigued, difficulty concentrating, irritability, muscle tension and sleep disturbance
Panic disorder	The presence of anxiety with recurrent panic attacks	Palpitations, sweating, trembling or shaking, sensations of shortness of breath, feeling of choking, chest pain/discomfort, nausea, feeling dizzy or lightheaded, feelings of unreality, fear of losing control, fear of dying, tingling sensations, chills or hot flushes
Phobic disorders	Includes agoraphobia and social phobia, as well as a range of other phobias	Marked or persistent fear of one or more social or performance situations Exposure invariably invokes anxiety or panic attack Social or performance situations are avoided (or endured with intense anxiety or distress)

MDD: major depressive disorder; DD: dysthymic disorder. [#]: based on the National Institute for Health and Clinical Excellence guidelines; clinical guideline 90 [9], clinical guideline 91 [10], and clinical guideline 113 [11]. Data from [8].

rates of anxiety in COPD patients between 10% and 15.8% compared with lifetime rates in the general public of 3.6% to 5.1% [17]. Prevalence of panic attacks ranged between 8% and 37%, which is several times higher than found in the general population [17]. Anxiety-related disorders are often characterised by chronicity [18], relapses [19] and periods of disability [20].

It is important not to neglect the co-occurrence of depression and anxiety, reported in 22–48% of COPD patients [7]. Furthermore, depression and anxiety are often comorbid with other medical conditions, compounding disability and imposing even greater burden on the daily lives of both patients and healthcare services [21]. Fears related to the disease and enhanced by depression have been identified as major COPD-specific comorbid symptoms [22].

A number of variables have been associated with risk for depression and/or anxiety in COPD patients (table 2). Respiratory symptoms, in particular dyspnoea, tend to be the most powerful predictors of symptoms of depression and anxiety [7, 15]. The risk for depression is higher in patients with more severe COPD compared to control subjects [24], and prevalence is highest in oxygen dependent patients as well as those recovering from an acute exacerbation [23]. The odds of depression are significantly greater amongst patients who live alone or who are not married [15, 24], have limited airflow reversibility and have a greater impairment to physical functioning [24, 25]. Psychological distress is higher amongst COPD patients with unsupportive family relationships [26]. High-quality prospective [27] and meta-regression studies [16] have found that subjective measures, such as health-related quality of life (HRQoL) and patient-reported symptoms, are stronger determinants of depression than clinical and physiological measures. However, there is still uncertainty about the importance of other risk factors including (younger) age, female sex, smoking and markers of socioeconomic status, with some studies reporting increased risk related to these variables and other studies reporting no difference in risk [7, 15, 16, 24, 28].

Aetiology and pathogenesis

Numerous theoretical models have been proposed to elucidate the relationship between depression, anxiety and COPD. Many of these theories describe the pathogenic mechanisms associated with these relationships as bidirectional and complex.

Theories relating to depression in COPD have focussed on mechanisms associated with the complicated role of smoking, hypoxia, systemic inflammation and the impact of illness on patients' lives.

Smoking is not only the most important risk factor in the development of COPD, but it also has a complex relationship with mental health. Numerous studies have concluded that depression and anxiety are risk factors for initiating tobacco smoking, often in adolescence or early adulthood [29, 30]. Smoking rates amongst those with severe mental illnesses, such as major depression, are high [31]. A large multinational study reported the existence of a diagnosis of major depression in 23.7% of current smokers compared with only 6.2% in those who never smoked [32], whilst other studies have found a significantly increased risk of depression in smokers compared with nonsmokers [33]. Moreover, smokers with a history of depression and/or anxiety are more likely to experience worse nicotine withdrawal and have significantly more failed cessation attempts [34, 35]. A number of studies have found that smoking cessation itself may induce depressive

Table 2. Risk factors for depression or anxiety in patients with COPD

Consistent associations	Mixed or inconsistent associations
Severe dyspnoea	Forced expiratory volume in 1 second
Health-related quality of life	Low body mass index
Self-reported impairment to physical functioning	Medical comorbidities
Long-term oxygen therapy	Age
Acute exacerbation	Sex
Limited airflow reversibility	Socioeconomic status
Lives alone/not married	Smoking status
Unsupportive family relationships	

Reproduced and modified from [23] with permission from the publisher.

symptoms in some individuals, particularly smokers with a history of depression [36, 37], leading to the suggestion that nicotine has an effect on mood *via* the cholinergic receptors [38].

A twin study suggested that shared genetic factors link smoking and depression [39]. More recently, variation in a serotonin transporter gene found to be associated with depression and tobacco smoking led the authors to postulate a genetic role in COPD pathogenesis [40].

Hypoxia is a consequence of both smoking and COPD and is itself recognised as playing a role in the development of depression, psychomotor slowing and memory problems [41]. One proposed pathogenic mechanism behind the neurological and psychiatric changes relates to oxygen insufficiency in the periventricular and subcortical regions of the brain leading to similar changes to those evident on the magnetic resonance imaging scans of depressed individuals [42], with white matter damage and vascular endothelial damage [41]. Neuropsychological impairments and depression may both be linked to the same pathophysiological brain disturbances in COPD patients [43]. Additionally, impairments in attention and memory have been associated with abnormal blood gas results [44]. A recent review of the effects of hypoxia on cognition pointed to subcortical mild cognitive impairment, which is characterised by bradyphrenia, memory impairment, verbal language loss, attention disturbance, and emotional and psychiatric problems including apathy and depression [45].

COPD is an inflammatory disorder [3] with systemic manifestations attributed to systemic “spill-over” [46, 47]. This inflammation has been linked with a variety of COPD phenotypes including depression [15, 48]. Moreover, depression itself is associated with impaired immune function [49] and increased susceptibility to infections [50] which may, at least partly, explain the observed higher incidence of infective exacerbations in patients with COPD and comorbid depression [51]. Whilst some studies demonstrating associations between inflammatory biomarkers in COPD patients and depressive symptoms give support to these theories [52, 53], many of these studies are limited by methodological concerns such as small sample sizes and a lack of adjustment for potential confounders. A large study, accounting for these confounders, demonstrated significant associations between inflammatory biomarkers and depression, providing further support for the shared inflammatory pathway hypothesis [54]. However, other studies, including an observation of the large ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) cohort, have not revealed any significant associations between inflammatory biomarkers and depression [27], leading some to conclude that the evidence for the COPD inflammation–depression hypothesis is not yet clear [55].

Several theories of depression in COPD patients focus on the impact of the illness on the lives on individuals. These models, summarised by NORWOOD [42], suggest that grief and functional loss contribute to depression [56], propose that poor coping and low self-efficacy skills decrease mastery and adjustment to COPD whilst increasing the likelihood of depressive symptoms [57], and indicate that the perception of positive social and instrumental support for COPD mediates the impact on depression [58, 59].

Dysfunctional breathing associated with COPD and panic forms the basis of hyperventilation models of anxiety [41]. Since both dyspnoea and panic are linked with hyperventilation, this model also postulates that the resulting hypocapnia will further aggravate breathlessness and anxiety. Hyperventilation is proposed to induce frightening symptoms of hypocapnia, as well as protect against the feared symptoms of suffocation associated with hypercapnia [41].

The carbon dioxide hypersensitivity model [60] is based on results demonstrating this association in COPD patients [61] and those with panic disorder [62]. It was posited that a “suffocation false alarm” is triggered by hypersensitive brain chemoreceptors, resulting in panic [60]. Both carbon dioxide and lactate may share mechanisms of action and induce significant ventilatory symptoms [63], suggesting physiological and neuroanatomical overlaps. Some support for the carbon dioxide and lactate models comes from observations that lactate can induce panic attacks in panic disorder patients who, in turn, had higher lactate levels following hyperventilation and lactate-induced panic than those found in patients without panic disorder [63].

The hyperventilation and carbon dioxide hypersensitivity models led to considerable research regarding the mechanisms of panic attacks with growing evidence of respiratory and non-respiratory subtypes of panic attacks [64]. Studies in which a variety of carbon dioxide/oxygen mixtures or hyperventilation and breath-holding tasks were administered to alter carbon dioxide levels were included in this review [64]. In these studies, panic disorder patients classified as “respiratory subtypes” experienced significantly more panic attacks than “non-respiratory subtypes”.

The cognitive behavioural model of anxiety in COPD suggests that bodily sensations induced by dyspnoea and dysfunctional breathing are interpreted in a fear-provoking manner. These catastrophic cognitions are proposed to be based on a perception of threat and impending doom, leading to heightened physiological arousal which, in turn, adds to the symptom cycle [65]. In addition, negative cognitions about illness symptoms may trigger frustration and even anger, resulting in higher physiological arousal, dyspnoea and anxiety [66]. COPD patients with panic disorder have significantly more negative cognitions than those without panic disorder despite similar pulmonary function, leading some authors to suggest that anxiety in the former group is based more on dysfunctional thinking rather than disease severity [67].

Impact

Although the high prevalence of depression and anxiety and their consequences are now well known, less appreciation is afforded to the impacts of these problems amongst COPD patients. Depression and anxiety are associated with clinically significant negative impacts and worse health outcomes across a number of domains. As will be discussed, depression and anxiety are linked with increased COPD symptom burden and exacerbation rates, impaired physical functioning and HRQoL, lower levels of adherence with recommended treatments, increased hospitalisation, length of hospital stay and hospital re-admission, worse treatment outcomes, and increased mortality.

Research has identified a relationship between severe COPD and depression. Prevalence of depression increases with the severity of COPD [68], and patients with severe COPD with depression have a higher likelihood of exacerbations [69] and frequent readmissions [70], and worse survival [71].

Depression is associated with numerous functional measures of COPD, including dyspnoea and disability, even after adjusting for COPD severity [43, 72]. Depressed COPD patients demonstrate lower functional and health status compared to those who present with no psychological issues [73]. Anxiety has also been linked to significantly lower functional status amongst COPD patients [67]. The level of disability in COPD patients has been related to the level of subjective anxiety-related symptoms; however, there does not appear to be a clear or consistent association between anxiety and some objective measures of functional capacity [74]. Nevertheless, depression and anxiety may be better predictors of overall functional ability than physiological capability in COPD patients [75].

In COPD, anxiety has also been linked to greater disability [76], an increased frequency of hospital admissions for acute exacerbations [77] and dyspnoea [78]. Anxiety symptoms in patients with COPD may include hyperventilation [79], and this has been associated with dynamic hyperinflation which further increases dyspnoea and exercise intolerance [80].

HRQoL can be severely restricted in those who suffer from COPD, and this is exacerbated by the presence of depression and anxiety [81]. Depression and anxiety strongly impair health status and HRQoL in patients with COPD and this impairment remains when studies have controlled for both severity of COPD and socio-demographic confounders [68]. Studies using multivariate models to explore the relationship between HRQoL and depression and anxiety symptoms have found that the relationship is modified by sociodemographic factors (age, work status and socioeconomic status), smoking status, severity of COPD and the presence of other comorbidities [82].

Depressive symptoms have also been directly linked to social functioning which, in turn, can be a determinant in HRQoL [71]. There may be additional social problems such as an increase in

significant marital issues [41]. Partners of patients with COPD often face an additional caring burden, and where patients feel they are no longer able to take care of tasks they once did, this correlates with a lower HRQoL for both patients and their partners, and higher scores for depression [83]. Although not formally explored in COPD, the stress of caring or the frustration of having the disease may provoke verbal or even physical abuse to patients or carers.

Both COPD and depression have some of the greatest influences upon disruption to disability-adjusted life years [84], thus the combination of the two can potentially have devastating effects on sufferers. The reduction in emotional functioning due to psychological factors such as depression may not only be a predictor of a greater need for healthcare utilisation but also less medication compliance, which in itself can be a critical factor in exacerbation rates and even survival [71].

Some studies indicate that engagement and adherence with best-practice treatments for COPD are negatively affected by psychological distress. A recent systematic review evaluating the link between depression and completion rates in pulmonary rehabilitation concluded that depression at baseline reduced the odds of programme completion [85]. This conclusion is of direct relevance since high rates of mental health problems have been reported amongst patients with COPD referred for pulmonary rehabilitation [86]. Additionally, depression has been associated with lower adherence to correct nebuliser use [87]. Some studies have demonstrated a relationship between depression and decreased preference for resuscitation in COPD patients on long-term oxygen therapy [88]. However, the evidence is not yet clear as other studies have found an absence of this association [89]. Additionally, a recent study demonstrated that these patient preferences may change regularly during the course of advanced COPD and that these variations can be predicted by changes in a number of variables including anxiety and depression [90].

Hospital readmissions, especially for acute exacerbations in COPD, can occur in up to 60% of patients within the first year of an index admission [91]. COPD patients who were readmitted to hospital have been shown to suffer poorer HRQoL and greater levels of depression and anxiety [91].

Higher levels of distress caused by disruption to psychological wellbeing have been reported to relate to greater numbers of hospital admissions for treatment of exacerbations of COPD, significantly increased duration of hospital stay and greater risk of subsequent hospitalisation [41, 74, 91–93]. COPD patients with depression are also at greater risk of hospitalisation during follow-up assessments [94]. Readmissions to a hospital setting, as well as greater chances of exacerbations [70] and worse survival rates [71], are observed in those patients who suffer from COPD with depressive symptoms.

In a national sample of hospitalised COPD patients [95], existing depression and anxiety was not only a risk factor for subsequent readmission to hospital, but also for higher 30-day mortality. Increased risk of mortality associated with depression is consistent with other reports of inpatient samples, although it is less consistent amongst studies involving outpatient samples. Some studies have found depression to be a significant predictor of mortality in both stable and unstable COPD patients even after adjustment for other known risk factors [71, 96, 97]. Furthermore, a recent household probability sampling method used in the USA identified increased odds of suicidal ideation and behaviour among adults with COPD compared to those without COPD, even after adjustments were made for depression, panic disorder and demographics [98].

Like depression, anxiety can influence the course of COPD. Some studies have reported that the presence of anxiety leads to greater frequency of hospital admissions and length of stay, an increased need for medication, reduced physical mobility, increased fatigue and greater levels of dyspnoea [67, 99]. Anxiety has also been linked to an overall increase in the length of exacerbations [75].

Assessment

Diagnostic challenges regarding anxiety and mood disorders remain problematic in the COPD population. The accuracy and frequency of appropriate diagnostic procedures in relation to

anxiety and depression continues to be an area that lacks attention [24, 27, 74]. Consequently, some caution is required in the interpretation and generalisation of the extent of depression and anxiety in COPD. Most of the studies of depression and anxiety in patients with COPD use self-reported screening questionnaires to determine the presence of symptoms as a surrogate measure of the existence of a mental disorder rather than the gold standard of structured interviews for clinical diagnosis performed by a trained mental health professional. Clearly, the distinction between screening and diagnosis of a mental health disorder is often blurred in the literature and this may have consequences for clinical application. Diagnosis of a specific anxiety or mood disorder should be made by a qualified mental health professional and should be based on the criteria listed in the DSM-IV (table 1).

Whilst symptoms of depression and anxiety are prevalent amongst COPD patients, screening for these problems remains a far too infrequent practice [27, 74]. This lack of integration into standard practice is evident despite the availability of numerous instruments and the relative ease of screening for symptoms of distress in comparison with a specialised diagnostic interview to ascertain a specific disorder subtype [9, 10]. The lack of specificity and detail regarding screening and diagnosis of anxiety and depression in clinical guidelines for the management of COPD [3] may be a factor contributing to the lack of practice uptake. Conversely, there is a lack of evidence concerning the efficacy of screening for anxiety and depression in terms of implementing relevant interventions to address these problems during the early stages of COPD [100].

The benefits of self-reported measures include reduced costs and ease of administration which, in turn, increase the likelihood of larger sample achievement. However, there are some noteworthy limitations since comparisons across studies might be impacted by the use of different instruments that use dissimilar cut-off scores or symptom time-frames. In addition, there is overlap between items designed to measure depression and anxiety, as well as those that measure symptoms of COPD, potentially leading to an overestimation of the prevalence of mental disorders. Consequently, some authors have gone to the extent of explicating the factors that make a specific mental disorder distinguishable from somatic overlap in the COPD population [101]. This detailed information will ultimately assist the diagnostic process.

There are a number of advantages and disadvantages associated with the various screening scales for anxiety and depression (table 3). It should be noted, however, that none of the screening scales are diagnostic, nor are these tools designed with such a purpose, and responses to items on these questionnaires often include some somatic and ageing overlap (e.g. fatigue). Similarly, these limitations are evident in emotion-based subscales of respiratory-specific and generic HRQoL measures. Furthermore, these screening tools do not distinguish between primary and secondary diagnoses of mood or anxiety disorders. The Hospital Anxiety and Depression Scale (HADS) is the most commonly cited of these screening scales in COPD studies. It has been explicitly designed for use with hospital populations and is, therefore, structured to reduce the influence of somatic overlap, although some commonality still exists. It has been validated in the COPD population, includes separate anxiety and depression components and can be used in primary care [102]. However, evidence for the greater ability of HADS to assess depression compared with other standard scales has not yet been established [103, 104]. Other screening tools cited in COPD research include the Beck Depression Inventory (BDI), the Hamilton Anxiety Rating Scale (HARS) and the CES-D. These tools provide advantages in terms of detail regarding depressive symptoms and severity. Furthermore, they have been widely used in many populations and appear to be good indicators of possible depression or anxiety in COPD [24]. The Geriatric Depression Scale (GDS) has advantages in terms of being validated in an elderly population, although, like the other anxiety and depression screening questionnaires, there is no evidence for superiority of one over another in terms of validity, reliability or case-finding in non-COPD or COPD populations.

Nevertheless, higher scores on psychological distress screening scales are of direct relevance to management since there is a strong positive relationship between self-reported severe symptoms and the existence of a mental disorder [9, 10]. Referral to a mental health specialist is recommended when higher scores on such scales are noted, as this allows the possibility of a

Table 3. Common screening instruments for assessment of symptoms of anxiety and/or depression

Screening instrument	Length	Mode of administration	What is measured
Beck Depression Inventory (BDI)	21 items	Interviewer administered (can be self-reported)	A score of 21 or over is indicative of the presence of depression Severity of depression ranges from minimal depressive symptoms (0–9), through to severe depression (scores of 30 to 63) The BDI can distinguish between different subtypes of depressive disorders, such as major depression and dysthymia Response categories indicate the frequency of occurrence of each item, and are scored on a four-point scale Higher scores indicate more depressive symptoms A score of 16 or higher has been used extensively as the cut-off point for high depressive symptoms
Centre for Epidemiological Studies of Depression (CES-D)	20 items (or eight-item short form)	Self-reported or interviewer administered	Screening measure for late life depression
Geriatric Depression Scale (GDS)	15 items	Self-reported and i Phone app	Severity of anxiety symptoms
Hamilton Anxiety Rating Scale	14 items	Self-reported	Identifies (possible and probable) causes for anxiety disorders and depression
Hospital Anxiety and Depression Scale (HAD)	14 items	Self-reported	Provides a diagnosis of disorder Considered the gold standard for research diagnosis of depression
Structured Clinical Interview for DSM disorders (SCID-I)	Variable depending on modules included	Interviewer administered	A total score provides indicative ranges for depression severity Each item is scored on a four-point scale Most people with depression score between 50 and 69, while a score of 70 and above indicates severe depression
Zung Depression Scale (ZDS)		Self-reported	

DSM: Diagnostic and Statistical Manual of Mental Disorders.

comprehensive, gold-standard diagnostic assessment [9, 10]. Accurate mental health assessment is a valuable tool informing the management of an individual with both COPD and mental disorder(s). Consequently, treatment methods can be individually tailored and selected to address specific mental health disorders and related psychosocial issues. Mental health clinical guidelines state that management is optimised when specific subtypes are accurately assessed and matched with best-practice treatment modalities [11].

Treatment

Besides pulmonary rehabilitation, which is unfortunately available for only a small percentage of COPD patients [105], treatment options for mental health issues are less frequently documented for patients with COPD [106]. This section provides a brief overview of current therapy options available for patients with COPD and mental health problems.

Reported effects for the different treatment options of mental health problems in COPD are often mixed and direct comparisons between different treatment options are almost non-existent [100, 107]. Therefore, further investigation with high methodological quality studies is required [100].

Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is a structured psychological intervention in which the patient works collaboratively with the therapist to identify the types and effects of thoughts, beliefs and interpretations on current symptoms, feelings, states and/or problem areas [108]. In CBT, patients will develop skills to control their symptoms and manage their disorder by utilising a combination of behavioural and cognitive techniques to counteract problematic thoughts, beliefs and interpretations related to the target symptoms and problems [9, 10, 109].

The National Institutes for Health and Clinical Excellence (NICE) guidelines recommend low intensity CBT-based psychosocial interventions (*e.g.* computerised CBT or a structured group physical activity programme using principles of CBT) for people with mild-to-moderate depression and/or anxiety [10], and high-intensity psychological intervention using CBT in combination with medication for people with moderate-to-severe depression [10].

CBT has gained prominence because of its effectiveness in achieving behavioural change within a limited number of sessions [109–111]. Whereas CBT has promising potential to reduce mental health symptoms in patients with COPD, there is still heterogeneity in both the reported interventions and their effectiveness [12, 101, 107, 112–114]. Therefore, there is limited evidence that CBT contributes to significant reductions in depression and/or anxiety amongst COPD patients. Further randomised controlled trial (RCT) studies are necessary to provide evidence on the effectiveness of CBT in COPD patients [112].

Behavioural therapy may be as effective in reducing depressive symptoms as the more comprehensive CBT model [115]. In this approach, a short-term structure is developed that could, for example, include organising social activities into the daily plan to alleviate the isolation that is often a symptom of depression and illness.

Interpersonal psychotherapy

Interpersonal psychotherapy (IPT) makes an assumption that the development of clinical depression occurs in the social and interpersonal context and that the onset, response to treatment and outcomes are influenced by the relationships between the patient and significant others [116]. The therapy focuses upon unresolved loss or grief, disputes, role transitions and social deficits [117].

Among psychotherapeutic options, CBT and IPT have the strongest evidence of treatment efficacy with major depressive disorder [10, 108]. IPT has shown positive results in people with social anxiety disorders [118] and depressive symptoms in older adults [119]. Whereas there are logical connections between IPT, depression, COPD and ageing issues, to date no studies have evaluated the effectiveness of IPT in COPD patients with mental health problems.

Pharmacological treatments

Due to a paucity of high-level evidence for antidepressant therapy to overcome anxiety and depression disorders in patients with COPD [120–122], many of our recommendations are drawn from how mental health disorders in older patients and those with other chronic diseases are managed.

Medications used in standard clinical practice for depression include antidepressants, benzodiazepines, azapirones and, less commonly, antipsychotic agents and anticonvulsants [120]. The antidepressants are further classified into groups based on which chemicals in the brain they affect. The main classes of antidepressants include the following. Non-selective antidepressants: tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs); and selective antidepressants: selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline re-uptake inhibitors (SNRIs), noradrenaline and dopamine re-uptake inhibitors (NDRIs), mianserin (a tetracyclic antidepressant), mirtazepine and venlafaxine, which all have multiple receptor effects [120]. A recent systematic review addressing antidepressants for depression in people with chronic medical

conditions found pooled efficacy after 6–8 weeks of treatment in favour of antidepressants (OR 2.33, 95% CI 1.80–3.00, $p < 0.00001$), and this applied to all classes of drug evaluated [123]. This review attempted some subgroup analysis, but there were only three RCTs found in COPD, preventing useful meta-analysis.

SSRIs are generally considered as preferred first-line agents for the control of symptoms of depression in patients with COPD [9], with some evidence pointing to improved depression scores and HRQoL outcomes [124, 125]. SSRIs are relatively selective in their pharmacological effects [126]. Either venlafaxine or mirtazepine are considered alternative drugs for patients who are not responsive to SSRIs or patients who previously had a good response to these drugs [127]. TCAs and MAOIs can also be used, but with caution [128] because of clinically significant pharmacodynamic interactions with many medications frequently prescribed to elderly patients [128], as well as those with chronic illnesses (table 4).

As is the case with depression, there is no high-level evidence for benefits from pharmacotherapies to treat anxiety in patients with COPD [9], even though antidepressants and benzodiazepines are commonly used. In a recent systematic review of RCTs of drugs for anxiety disorders in COPD patients, only four trials meeting inclusion criteria were found. These were conducted in small populations with short follow-up using a range of drugs, and the heterogeneity prevented meta-analysis of efficacy or tolerability [120]. Whereas there are indications that they might be effective to control anxiety symptoms in patients with COPD [120], no RCTs are available to assess the efficacy of benzodiazepines in this population. Furthermore, there are prevalent concerns that this class of drugs is associated with reduced respiratory drive, raising fears of hypoventilation and respiratory failure. Most observations relate to over-dosage or use as anaesthetic agents but caution is advisable, especially in patients already with a compromised respiratory drive. Current recommendations in anxiety management are, therefore, for CBT to be used as a front-line treatment for generalised anxiety disorder and generalised social anxiety disorder [9] and to add SSRIs when CBT is ineffective or unsuitable. If there is no improvement in the first 3 months an alternative SSRI, or imipramine or venlafaxine is recommended for generalised anxiety disorder, and either sertraline, fluvoxamine or venlafaxine for generalised social anxiety disorder [9]. Benzodiazepines have a high risk of tolerance and dependence, and should only be used for short-term periods and/or for acute exacerbation of anxiety symptoms; they should not be used in patients who have had hypercapnia.

Side-effects of antidepressant medications are not insignificant, and include dry mouth, sexual dysfunction, dizziness, hypotension, nausea, appetite change, constipation, insomnia, sedation and headache [123]. Some (such as dry mouth) may compound adverse effects of medications used for COPD, notably anti-muscarinic agents. The range of adverse effects with each drug group are summarised in table 5.

Pulmonary rehabilitation

Pulmonary rehabilitation has extensive evidence supporting its benefits, and is a highly recommended core component of treatment in COPD patients [3]. Pulmonary rehabilitation involves assessment of patient problems and goals, exercise training, education, nutritional intervention and psychosocial support [105, 131] with the aim of restoring the patient to the highest possible level of independent functioning [132].

Benefits from pulmonary rehabilitation identified in a meta-analysis of RCTs include improvements in HRQoL and exercise tolerance, as well as reductions in dyspnoea and fatigue [133]. Other benefits include reduced hospitalisation for COPD exacerbations and therefore healthcare utilisation costs [134]. Pulmonary rehabilitation can also reduce symptoms of both depression and anxiety in patients with mild [135] and moderate-to-severe COPD [3, 136]. A recent review provided further evidence of lower depression and improved mood scores after pulmonary rehabilitation in patients with COPD and comorbid depression [137]. In addition, a recent large study concluded that pulmonary rehabilitation has positive effects on depression and anxiety scores in patients with COPD. The authors also pointed out that the actual effect of pulmonary rehabilitation on mental

Table 4. Important adverse effects from antidepressant therapy

Adverse effects	SSRI	Venlafaxine	Mirtazepine	Tricyclic antidepressants	Monoamine oxidase inhibitors
Agitation	++	+/-	+/-	++	++
Anti-cholinergic delirium	+/-	+/-	+/-	++	+/-
Anxiety	++	++	+/-	++	+/-
Blurred vision	+/-	+/-	+/-	++	+
Cardiac dysrhythmias	+	+	+/-	++	+
Confusion	+	+/-	+/-	++	+/-
Constipation	+/-	+	+/-	++	++
Diarrhoea	++	+/-	+/-	+/-	+/-
Dizziness	++	++	+/-	++	+/-
Dry mouth	++	+	+/-	++	++
Elevated serum aminotransferases	+/-	+/-	+/-	+/-	++
Fatigue	+/-	++	+/-	+/-	++
Headache	++	++	+/-	+/-	++
Hypertension	+/-	++	+/-	+/-	+/-
Decrease lacrimation	+/-	+/-	+/-	++	+/-
Myoclonus, twitching and tremor	++	++	+/-	++	++
Myalgia	++	+/-	+/-	+/-	+/-
Nausea and vomiting	++	++	+/-	+	+/-
Orthostatic hypotension	+	+	+/-	++	++
Peripheral oedema	+/-	+/-	++	+/-	+
Rhinitis	++	+/-	+/-	+/-	+/-
Sedation and/or drowsiness	++	+	++	++	++
Sexual dysfunction	++	+	+/-	++	++
Skin problems	++	++	+/-	+	+
Sleep disturbance	++	+	+/-	++	++
Sweating	++	++	+/-	++	+
Urine hesitancy or retention	+/-	+/-	+/-	++	+/-
Weakness	++	+/-	++	+/-	++
Weight gain	++	+/-	++	++	++
Weight loss	++	++	+/-	+/-	+/-

SSRI: selective serotonin re-uptake inhibitors. Frequency of adverse effects: +/-: rare (incidence of <0.1%) or non-reported; +: infrequent (incidence of 0.1–1.0%); ++: common (incidence of ≥ 1%). This classification should not be interpreted too strictly as the incidence of adverse effects often depends on the risk factors presented by a specific population and the dose of the drugs administered. Based on data from [127]. Reproduced from [4] with permission from the publisher.

health scores might even be under-estimated, because of the exclusion of COPD patients having raised depression and/or anxiety scores in many studies [138].

Which specific component(s) of pulmonary rehabilitation confers psychosocial benefits for COPD patients remains unclear [100, 139]. This knowledge may inform the appropriate selection of effective components, which may be useful given the known limited access to comprehensive pulmonary rehabilitation for patients [100, 105]. In theory, combining CBT with pulmonary rehabilitation may provide even greater benefits by decreasing respiratory symptoms and psychological distress, as well as improving HRQoL; however, convincing evidence for this is still lacking. Furthermore, elements of CBT are already evident in the practice of pulmonary rehabilitation. It should be noted that when specific psychological interventions are included in pulmonary rehabilitation, the involvement of a mental health specialist for this task is highly recommended. It has been demonstrated that improvements in mental health symptoms following PR are greater in patients with low exercise capacity, lower self-efficacy and clear symptoms of anxiety or depression. This highlights the importance of characterising patients

Table 5. Side-effects of antidepressant drug therapy in patients with COPD and comorbid anxiety and/or depression

First author [ref.]	Study type	Subjects n	Medication	Reported side-effects
GORDON [122]	Cross-over trial	13	Desipramine (TCA)	Intolerable side-effects [#] (n=2), dry mouth [¶] , fatigue [¶] and tremor [¶]
LIGHT [121]	Cross-over trial	12	Doxepin (TCA)	Blurred vision (n=5), drowsiness (n=3), dry mouth (n=2) and headache (n=1)
BORSON [43]	RCT	36	Nortriptyline (TCA)	Dry mouth (n=1), sedation (n=1) and orthostatic hypotension (n=1)
SINGH [129]	RCT	11	Buspirone (azapirone)	Nausea, diarrhoea and dyspnoea (n=2), dizziness and fatigue (n=1)
LACASSE [125]	RCT	23	Paroxetine (SSRI)	Somnolence (n=5), tremor (n=2), constipation (n=2), nausea (n=2), headache (n=2), dry mouth (n=1) and taste perversion (n=1)
SUBBE [130]	RCT	8	Citalopram (SSRI)	Insomnia, restlessness and worsening anxiety (n=1) and minor side-effects (n=6)
EISER [124]	RCT	28	Paroxetine (SSRI)	Nausea and vomiting (n=4)

RCT: randomised controlled trial; TCA: tricyclic antidepressants; SSRI: selective serotonin re-uptake inhibitors.
#: no further explanation was provided about the nature of the side-effects; ¶: no number-wise distribution was provided for these side-effects.

before entry to pulmonary rehabilitation to allow better targeting of psychological interventions [138, 140].

Finally, the relationship between fatigue and important outcomes in COPD (e.g. disease severity and hospital admissions) is currently attracting research interest [141]. However, the usefulness of targeting fatigue in pulmonary rehabilitation and the possible influence on mental health outcomes still needs to be explored.

Relaxation therapy

Relaxation can be used as an adjunct to other forms of therapy such as CBT, pulmonary rehabilitation and self-management programmes. Relaxation therapy encompasses a wide range of techniques such as breathing exercises, progressive muscle relaxation, isometric muscle relaxation, biofeedback, hypnosis and meditation. The purpose of these techniques is to facilitate the relaxation response by effectively managing the group of physiological changes that accompany anxiety, which allows regulation of the sympathetic nervous system and management of the stimulation of certain regions of the hypothalamus [142].

A review of relaxation therapy concluded that it is effective in reducing hypertension, insomnia, anxiety, pain and medication use across multiple populations, diagnostic categories and settings [3]. A meta-analysis in COPD patients found statistically significant beneficial effects on both dyspnoea and psychological wellbeing [144].

Palliative care

Palliative care is medical care provided by an interdisciplinary team, including the professions of medicine, nursing, social work, chaplaincy, counselling, nursing assistants and other healthcare professions focused on the relief of suffering and support for the best possible quality of life for patients facing serious life-threatening illness and their families [145]. It aims to identify and address the physical, psychological, spiritual and practical burdens of illness [145].

Successful approaches in the palliative setting to the assessment and management of pain and some physical and psychological symptoms have been established in controlled trials [6].

Promising improvements in mental health were also found for COPD patients in a study of an intensive home-based case management programme which included support for their psychological needs [147].

Self-management programmes

Self-management programmes have been developed for a variety of medical populations and have been implemented in a wide range of clinical and primary care settings. These aim at teaching skills needed to carry out medical regimens that are specific to a long-term disease and guide health behaviour change to help patients control their disease and improve their wellbeing [148]. Training of self-management skills is increasingly incorporated in pulmonary rehabilitation programmes [105].

Generic self-management programmes focus not so much on the problems related to one specific disease, but on those encountered during the course of any chronic disease, such as fatigue, pain and anxiety. Beneficial effects of these programmes on wellbeing have been reported in chronic disease populations [149, 150]. A recent study evaluated a nurse-administered minimal psychological intervention, including elements of CBT and self-management, in depressed elderly patients with COPD. Results showed significantly fewer depressive symptoms, reduced symptoms of anxiety and better HRQoL [114, 151]. COPD specific self-management programmes mainly focus on physiological outcomes and healthcare use [152]. The majority of studies that have included depression and/or anxiety as a secondary outcome have reported no effects [153, 154]. More research appears warranted in this area.

Recommendations

- 1) Screening patients with COPD for mental health symptoms should become standard practice.
- 2) Patients reporting severe depression or anxiety symptoms are more likely to have a mental disorder, so a more comprehensive diagnostic assessment is desirable in these patients.
- 3) Clinicians should be aware of the somatic overlap between depression and/or anxiety and COPD.
- 4) For COPD patients with mild-to-moderate anxiety and/or depression, low-intensity psychosocial interventions are recommended.
- 5) For COPD patients with moderate depression and/or anxiety, high-intensity psychological interventions using CBT in combination with antidepressant medications are warranted.
- 6) Among psychotherapeutic options, CBT and IPT have the strongest evidence of treatment efficacy with major depressive disorders in non-COPD populations.
- 7) Pharmaceutical agents should be prescribed if psychotherapeutic options do not control symptoms of depression or anxiety; benzodiazepines should be avoided and adverse effects of antidepressants should be monitored closely to avoid interactions with COPD drugs.
- 8) During the smoking cessation attempts of COPD patients, mental health problems need to be monitored and, when necessary, treated.
- 9) Growing evidence shows benefits of pulmonary rehabilitation for COPD patients with mental health issues, although it remains unclear what specific component(s) of pulmonary rehabilitation confer these psychosocial benefits.

Conclusion

While this chapter has addressed evidence related to prevalence, aetiology, impact, assessment and treatment of mental health disturbances in people with COPD, it is clear that some

recommendations for depression and anxiety treatment need to be based on other chronic disease populations, since there is little high-quality research conducted in COPD. Depression and anxiety are common in COPD, both individually and together, are particularly prevalent in patients with more severe COPD, can affect overall disease management, and have significant impacts on patients and carers. Therefore, mental health problems should be screened using the available well-validated tools in all patients with COPD, with referral for formal diagnosis by a mental health specialist recommended for those who have significant depression and/or anxiety symptoms. We have examined the treatments used for depression and anxiety in other populations, and made recommendations while emphasising the paucity of direct evidence of benefit in COPD populations. Therefore, there are many areas relating to the comorbidity of mental health disorders and COPD that warrant careful research.

Statement of Interest

P.A. Frith has received over the past 5 years educational grants and consultancy honoraria from Boehringer Ingelheim, Nycomed, Novartis and GlaxoSmithKline, as well as travel support to attend TSANZ from GSK, Novartis, Nycomed and to attend the ERS Congress from Novartis, Nycomed and Boehringer Ingelheim, none of whom stands to gain financially from this publication. He is an unpaid council member and Chair of the COPD Committee for the Australian Lung Foundation, which formulates educational support and guideline papers relating to COPD diagnosis and management, pulmonary rehabilitation and training for a wide range of health professional groups.

References

1. Moussas G, Tselebis A, Karkanas A, *et al.* A comparative study of anxiety and depression in patients with bronchial asthma, chronic obstructive pulmonary disease and tuberculosis in a general hospital of chest diseases. *Ann Gen Psychiatry* 2008; 7: 7.
2. Yohannes AM. Depression and COPD in older people: a review and discussion. *Br J Community Nurs* 2005; 10: 42–46.
3. Global Strategy for the Diagnosis, Management, and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2011. Available from: www.goldcopd.org Date last updated: February 21, 2012. Date last accessed: November 29, 2012.
4. Cafarella PA, Effing TW, Usmani ZA, *et al.* Treatments for anxiety and depression in patients with chronic obstructive pulmonary disease: a literature review. *Respirology* 2012; 17: 627–638.
5. National Institute for Health Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. NICE Clinical Guideline 101. London, NICE, 2010.
6. Holden L, Scuffham P, Hilton M, *et al.* Psychological distress is associated with a range of high-priority health conditions affecting working Australians. *Aust NZ J Publ Health* 2010; 34: 304–310.
7. Putman-Casdorph H, McCrone S. Chronic obstructive pulmonary disease, anxiety, and depression: state of the science. *Heart Lung* 2009; 38: 34–47.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edn. Washington, American Psychiatric Association, 2000.
9. National Institute for Health Clinical Excellence. Depression in adults: The treatment and management of depression in adults. NICE clinical guideline 90. London NICE, 2009.
10. National Institute for Health Clinical Excellence. Depression in adults with a chronic physical health problem: treatment and management. NICE clinical guideline 91. London, NICE, 2009.
11. National Institute for Health and Clinical Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. NICE clinical guideline 113. London, NICE, 2011.
12. Hynninen MJ, Breivite MH, Wiborg AB, *et al.* Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. *J Psychosom Res* 2005; 59: 429–443.
13. Yohannes AM, Willgoss TG, Baldwin RC, *et al.* Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psych* 2010; 25: 1209–1221.
14. Yohannes AM, Baldwin RC, Connolly MJ. Mood disorders in elderly patients with chronic obstructive pulmonary disease. *Rev Clin Gerontol* 2000; 10: 193–202.
15. Schane RE, Woodruff PG, Dinno A, *et al.* Prevalence and risk factors for depressive symptoms in persons with chronic obstructive pulmonary disease. *J Intern Med* 2008; 23: 1757–1762.

16. Zhang MWB, Ho RCM, Cheung MWL, *et al.* Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. *Gen Hosp Psychiatry* 2011; 33: 217–223.
17. Brenes G. Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. *Psychosom Med* 2003; 65: 963–970.
18. Gorman JM, Coplan JD. Comorbidity of depression and panic disorder. *J Clin Psychiatry* 1996; 57: Suppl. 10, 34–41.
19. Liebowitz MR. Panic disorder as a chronic illness. *J Clin Psychiatry* 1997; 58: Suppl. 13, 5–8.
20. Marcus SC, Olsson M, Pincus HA, *et al.* Self-reported anxiety, general medical conditions, and disability bed days. *Am J Psychiatry* 1997; 154: 1766–1768.
21. Lecrubier Y. The burden of depression and anxiety in general medicine. *J Clin Psychiatry* 2001; 62: Suppl. 8, 4–9.
22. Zöckler N, Rief W, Kühl K, *et al.* COPD-specific anxiety and depressive symptoms in COPD patients. *Pneumologie* 2012; 66: 290–296.
23. Maurer J, Rebbapragada V, Borson S, *et al.* Anxiety and depression in COPD. *Chest* 2008; 134: Suppl. 4, 43S–56S.
24. van Manen JG, Bindels PJE, Dekker FW, *et al.* Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. *Thorax* 2002; 57: 412–416.
25. Katz PP, Julian LJ, Omachi TA, *et al.* The impact of disability on depression among individuals with COPD. *Chest* 2010; 137: 838–845.
26. Holm KE, La Chance HR, Bowler RP, *et al.* Family factors are associated with psychological distress and smoking status in chronic obstructive pulmonary disease. *Gen Hosp Psychiat* 2010; 32: 492–498.
27. Hanania N, Mullerova H, Locantore N, *et al.* Determinants of depression in the ECLIPSE COPD cohort. *Am J Respir Crit Care Med* 2011; 183: 604–611.
28. Garvey C. Depression in patients with chronic obstructive pulmonary disease. *Postgrad Med* 2012; 124: 101–109.
29. Ferguson DM. Comorbidity between depressive disorders and nicotine dependence in a cohort of 16 year olds. *Arch Gen Psychiatry* 1996; 53: 1043–1047.
30. Patton GC, Hibbert M, Rosier MJ, *et al.* Is smoking associated with depression and anxiety in teenagers? *Am J Public Health* 1996; 86: 225–230.
31. Diaz FJ, James D, Botts S, *et al.* Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. *Bipolar Disord* 2009; 11: 154–165.
32. Wiesbeck GA, Kuhl HC, Yaldizli O, *et al.* Tobacco smoking and depression – results from the WHO/ISBRA study. *Neuropsychobiology* 2008; 57: 26–31.
33. Schneider C, Jick SS, Bothner U, *et al.* COPD and the risk of depression. *Chest* 2010; 137: 341–347.
34. Breslau N, Kilbey MM, Andreski P. Nicotine withdrawal symptoms and psychiatric disorders: findings from an epidemiologic study of young adults. *Am J Psychiatry* 1992; 149: 464–469.
35. Covey LS, Glassman AH, Stetner F. Cigarette smoking and major depression. *J Addict Dis* 1998; 17: 35–46.
36. Covey LS, Glassman AH, Stetner F. Depression and depressive symptoms in smoking cessation. *Compr Psychiat* 1990; 31: 350–354.
37. Glassman AH, Helzer JE, Covey LS, *et al.* Smoking, smoking cessation, and major depression. *JAMA* 1990; 264: 1546–1549.
38. Mineur YS, Picciotto MR. Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. *Trends Pharmacol Sci* 2010; 31: 580–586.
39. Kendler KS, Neale MC, MacLean CJ, *et al.* Smoking and major depression. A causal analysis. *Arch Gen Psychiatry* 1993; 50: 36–43.
40. Ishii T, Wakabayashi R, Kurosaki H, *et al.* Association of serotonin transporter gene variation with smoking, chronic obstructive pulmonary disease, and its depressive symptoms. *J Hum Genet* 2011; 56: 41–46.
41. Mikkelsen RL, Middelboe T, Pisinger C, *et al.* Anxiety and depression in patients with chronic obstructive pulmonary disease (COPD). A review. *Nord J Psychiatry* 2004; 58: 65–70.
42. Norwood R. Prevalence and impact of depression in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* 2006; 12: 113–117.
43. Borson S, Claypoole K, McDonald GJ. Depression and chronic obstructive pulmonary disease: treatment trials. *Semin Clin Neuropsychiatry* 1998; 3: 115–130.
44. Grant I, Heaton RK, McSweeney AJ, *et al.* Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med* 1982; 142: 1470–1476.
45. Areza-Fegyveres R, Kairalla RA, Carvalho CR, *et al.* Cognition and chronic hypoxia in pulmonary diseases. *Dement Neuropsychol* 2010; 4: 14–22.
46. Agustí A, Faner R. Systemic inflammation and comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2012; 9: 43–46.
47. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of “overspill” of inflammatory mediators from the lungs? Review of the evidence. *Thorax* 2010; 65: 930–936.
48. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; 33: 1165–1185.
49. Padgett DA, Glaser R. How stress influences the immune response. *Trends Immunol* 2003; 24: 444–448.
50. Cohen S, Tyrrell DA, Smith AP. Negative life events, perceived stress, negative affect, and susceptibility to the common cold. *J Pers Soc Psychol* 1993; 64: 131–140.

51. Laurin C, Labrecque M, Dupuis G, *et al.* Chronic obstructive pulmonary disease patients with psychiatric disorders are at greater risk of exacerbations. *Psychosom Med* 2009; 71: 667–674.
52. Al-shair K, Kolsum U, Dockry R, *et al.* Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. *Respir Res* 2011; 12: 1.
53. Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. *J Psychosom Res* 2002; 53: 873–876.
54. Eagan TM, Ueland T, Wagner PD, *et al.* Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study. *Eur Respir J* 2010; 35: 540–548.
55. Marinho PEM, Castro CM, Raposo MC, *et al.* Depressive symptoms, inflammatory markers and body composition in elderly with and without chronic obstructive pulmonary disease (COPD). *Arch Gerontol Geriatr* 2012; 54: 453–458.
56. Dunlop DD, Lyons JS, Manheim LM, *et al.* Arthritis and heart disease as risk factors for major depression: the role of functional limitation. *Med Care* 2004; 42: 502–511.
57. Kohler CL, Fish L, Greene PG. The relationship of perceived self-efficacy to quality of life in chronic obstructive pulmonary disease. *Health Psychol* 2002; 21: 610–614.
58. McCathie HC, Spence SH, Tate RL. Adjustment to chronic obstructive pulmonary disease: the importance of psychological factors. *Eur Respir J* 2002; 19: 47–53.
59. Penninx BW, van Tilburg T, Boeke AJ, *et al.* Effects of social support and personal coping resources on depressive symptoms: different for various chronic diseases? *Health Psychol* 1998; 17: 551–558.
60. Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. *Arch Gen Psychiatry* 1993; 50: 306–317.
61. Matthews AW. The relationship between central carbon dioxide sensitivity and clinical features in patients with chronic airways obstruction. *Q J Med* 1977; 46: 179–195.
62. Papp LA, Klein DF, Gorman JM. Carbon dioxide hypersensitivity, hyperventilation and panic disorder. *Am J Psychiatry* 1993; 150: 1149–1157.
63. Wemmie JA. Neurobiology of panic and pH chemosensation in the brain. *Dialogues Clin Neurosci* 2011; 13: 475–483.
64. Kircanski K, Craske MG, Epstein AM, *et al.* Subtypes of panic attacks: a critical review of the empirical literature. *Depress Anxiety* 2009; 26: 878–887.
65. Clark DM. A cognitive approach to panic. *Behav Res Ther* 1986; 24: 461–470.
66. Bailey PH. The dyspnea-anxiety-dyspnea cycle – COPD patients’ stories of breathlessness: “It’s scary when you can’t breathe”. *Qual Health Res* 2004; 14: 760–778.
67. Brenes GA. Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. *Psychosom Med* 2003; 65: 963–970.
68. Omachi TA, Katz PP, Yelin EH, *et al.* Depression and health related quality of life in chronic obstructive pulmonary disease. *Am J Med* 2009; 122: 778.
69. Jennings JH, Digiovine B, Obeid D, *et al.* The association between depressive symptoms and acute exacerbations of COPD. *Lung* 2009; 187: 128–135.
70. Cao Z, Ong KC, Eng P, *et al.* Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. *Respirology* 2006; 11: 188–195.
71. Ng TP, Niti M, Tan WC, *et al.* Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med* 2007; 167: 60–67.
72. Von Korff M, Katon W, Rutter C, *et al.* Effect on disability outcomes of a depression relapse prevention program. *Psychosom Med* 2003; 65: 938–943.
73. Tselebis A, Bratis D, Kosmas E, *et al.* Psychological symptom patterns and vital exhaustion in outpatients with chronic obstructive pulmonary disease. *Arch Gen Psychiatry* 2011; 10: 32.
74. Hill K, Geist R, Goldstein RS, *et al.* Anxiety and depression in end-stage COPD. *Eur Respir J* 2008; 31: 667–677.
75. Pommer AM, Pouwer F, Denollet J, *et al.* Managing co-morbid depression and anxiety in primary care patients with asthma and/or chronic obstructive pulmonary disease: study protocol for a randomized controlled trial. *Trials* 2012; 13: 6.
76. Aydin IO, Ulusahin A. Depression, anxiety comorbidity, and disability in tuberculosis and chronic obstructive pulmonary disease patients: applicability of GHQ-12. *Gen Hosp Psychiatry* 2001; 23: 77–83.
77. Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly outpatients with chronic obstructive pulmonary disease: prevalence, and validation of the BASDEC screening questionnaire. *Int J Geriatr Psychiatry* 2000; 15: 1090–1096.
78. Kellner R, Samet J, Pathak D. Dyspnea, anxiety, and depression in chronic respiratory impairment. *Gen Hosp Psychiatry* 1992; 14: 20–28.
79. Smith J, Albert P, Bertella E, *et al.* Qualitative aspects of breathlessness in health and disease. *Thorax* 2009; 64: 713–718.
80. Bernard S, Whittom F, Leblanc P, *et al.* Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 896–901.

81. Tsiligianni I, Kocks J, Tzanakis N, *et al.* Factors that influence disease-specific quality of life or health status in patients with COPD: a systematic review and meta-analysis of Pearson correlations. *Prim Care Respir J* 2011; 20: 257–268.
82. Balcells E, Gea J, Ferrer J, *et al.* Factors affecting the relationship between psychological status and quality of life in COPD patients. *Health Qual Life Out* 2010; 8: 108.
83. Meier C, Bodenmann G, Morgeli H, *et al.* Dyadic coping, quality of life and psychological distress among chronic obstructive pulmonary disease patients and their partners. *Int J COPD* 2011; 6: 583–596.
84. Regvat J, Zmitek A, Vegnuti M, *et al.* Anxiety and depression during hospital treatment of exacerbation of chronic obstructive pulmonary disease. *J Int Med Res* 2011; 39: 1028–1038.
85. Keating A, Lee A, Holland AE. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. *Chronic Resp Dis* 2011; 8: 89–99.
86. Troosters T, Casaburi R, Gosselink R, *et al.* Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 19–38.
87. Bosley CM, Corden ZM, Rees PJ, *et al.* Psychological factors associated with use of home nebulized therapy for COPD. *Eur Respir J* 1996; 9: 2346–2350.
88. Stapeleton RD, Nielsen EL, Engelberg RA, *et al.* Association of depression and life-sustaining treatment preferences in patients with COPD. *Chest* 2005; 127: 328–334.
89. Reinke LF, Slatore CG, Udris EM, *et al.* The association of depression and preferences for life-sustaining treatments in veterans with chronic obstructive pulmonary disease. *J Pain Symptom Manage* 2011; 41: 402–411.
90. Janssen DJ, Spruit MA, Schols JM, *et al.* Predicting changes in preferences for life-sustaining treatment among patients with advanced chronic organ failure. *Chest* 2012; 141: 1251–1259.
91. Coventry PA, Gemmell I, Todd CJ. Psychosocial risk factors for hospital readmission in COPD patients on early discharge services: a cohort study. *BMC Pulm Med* 2011; 11: 49.
92. Laurin C, Moullec G, Bacon SL, *et al.* Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. *Am J Respir Crit Care Med* 2012; 185: 918–923.
93. Laurin C, Moullec G, Bacon SL, *et al.* The impact of psychological distress on exacerbation rates in COPD. *Ther Adv Respir Dis* 2011; 5: 3–18.
94. Xu W, Collet JP, Shapiro S, *et al.* Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. *Am J Respir Crit Care Med* 2008; 178: 913–920.
95. Abrams TE, Vaughan-Sarrazin M, Vander Weg MW. Acute exacerbations of chronic obstructive pulmonary disease and the effect of existing psychiatric comorbidity on subsequent mortality. *Psychosomatics* 2011; 52: 441–449.
96. de Voogd JN, Wempe JB, Koëter GH, *et al.* Depressive symptoms as predictors of mortality in patients with COPD. *Chest* 2009; 135: 619–625.
97. Fan VS, Ramsey SD, Giardino ND, *et al.* Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. *Arch Intern Med* 2007; 167: 2345–2353.
98. Goodwin RD. Is COPD associated with suicide behavior? *J Psychiatr Res* 2011; 45: 1269–1271.
99. Howard C, Hallas CN, Wray J, *et al.* The relationship between illness perception and panic in chronic obstructive pulmonary disease. *Behav Res Ther* 2009; 47: 71–76.
100. Baraniak A, Sheffield D. The efficacy of psychologically based interventions to improve anxiety, depression and quality of life in COPD: a systematic review and meta-analysis. *Patient Educ Couns* 2011; 83: 29–36.
101. Livermore N, Sharpe L, McKenzie D. Prevention of panic attacks and panic disorder in chronic obstructive pulmonary disease. *Eur Respir J* 2010; 35: 557–563.
102. Kunik ME, Azzam PN, Soucek J, *et al.* A practical screening tool for anxiety and depression in patients with chronic breathing disorders. *Psychosomatics* 2007; 48: 16–21.
103. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004; 66: 802–813.
104. Thombs BD, Magyar-Russell G, Bass EB, *et al.* Performance characteristics of depression screening instruments in survivors of acute myocardial infarction: review of the evidence. *Psychosomatics* 2007; 48: 185–194.
105. Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.
106. Rabe KF, Hurd S, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532–555.
107. Fritzsche A, Clamor A, von Leupoldt A. Effects of medical and psychological treatment of depression in patients with COPD – a review. *Respir Med* 2011; 105: 1422–1433.
108. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. *Am J Psychiatry* 2000; 157: Suppl. 4, 1–45.
109. O’Hea E, Houseman J, Bedek K, *et al.* The use of cognitive behavioral therapy in the treatment of depression for individuals with CHF. *Heart Fail Rev* 2009; 14: 13–20.
110. Fekete EM, Antoni MH, Schneiderman N. Psychosocial and behavioral interventions for chronic medical conditions. *Curr Opin Psychiatry* 2007; 20: 152–157.
111. Thomas PW, Thomas S, Hillier C, *et al.* Psychological interventions for multiple sclerosis. *Cochrane Database Syst Rev* 2006; 1: CD004431.

112. Coventry PA, Gellatly JL. Improving outcomes for COPD patients with mild-to-moderate anxiety and depression: a systematic review of cognitive behavioural therapy. *Br J Health Psychol* 2008; 13: 381–400.
113. Kunik ME, Veazey C, Cully JA, *et al.* COPD education and cognitive behavioral therapy group treatment for clinically significant symptoms of depression and anxiety in COPD patients: a randomized controlled trial. *Psychol Med* 2008; 38: 385–396.
114. Lamers F, Jonkers CC, Bosma H, *et al.* Improving quality of life in depressed COPD patients: effectiveness of a minimal psychological intervention. *COPD* 2010; 7: 315–322.
115. Ekers D, Richards D, Gilbody S. A meta-analysis of randomized trials of behavioural treatment of depression. *Psychol Med* 2008; 38: 611–623.
116. Klerman GL, Weissman MM, eds. *New Applications of Interpersonal Psychotherapy*. Washington, American Psychiatric Press, 1993.
117. Judd F, Weissman M, Davis J, *et al.* Interpersonal counselling in general practice. *Aust Fam Physician* 2004; 33: 332–337.
118. Lipsitz JD, Gur M, Vermes D, *et al.* A randomized trial of interpersonal therapy *versus* supportive therapy for social anxiety disorder. *Depress Anxiety* 2008; 25: 542–553.
119. Miller MD. Using interpersonal therapy (IPT) with older adults today and tomorrow: a review of the literature and new developments. *Curr Psychiatry Rep* 2008; 10: 16–22.
120. Usmani ZA, Carson KV, Cheng JN, *et al.* Pharmacological interventions for the treatment of anxiety disorders in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011; 11: CD008483.
121. Light RW, Merrill EJ, Despars J, *et al.* Doxepin treatment of depressed patients with chronic obstructive pulmonary disease. *Arch Intern Med* 1986; 146: 1377–1380.
122. Gordon GH, Michiels TM, Mahutte CK, *et al.* Effect of desipramine on control of ventilation and depression scores in patients with severe chronic obstructive pulmonary disease. *Psychiatry Res* 1985; 15: 25–32.
123. Rayner L, Price A, Evans A, *et al.* Antidepressants for depression in physically ill people. *Cochrane Database Syst Rev* 2010; 3: CD007503.
124. Eiser N, Harte R, Spiros K, *et al.* Effect of treating depression on quality-of-life and exercise tolerance in severe COPD. *COPD* 2005; 2: 233–241.
125. Lacasse Y, Beaudoin L, Rousseau L, *et al.* Randomized trial of paroxetine in end-stage COPD. *Monaldi Arch Chest Dis* 2004; 61: 140–147.
126. Montgomery S. Efficacy and safety of the selective serotonin reuptake inhibitors in treating depression in elderly patients. *Int Clin Psychopharmacol* 1998; 13: Suppl. 5, S49–S54.
127. Rossi S, ed. *Australian Medicines Handbook* 2010. Adelaide, Australian Medicines Handbook Pty Ltd, 2010.
128. Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. *Drugs Aging* 2002; 19: 299–320.
129. Singh NP, Despars JA, Stansburg DW, *et al.* Effects of buspirone on anxiety levels and exercise tolerance in patients with chronic airflow obstruction and mild anxiety. *Chest* 1993; 103: 800–804.
130. Subbe C, Collier GM, Bedson E, *et al.* Pilot study to examine the effect of citalopram on health status, anxiety and depression in patients with chronic obstructive pulmonary disease, ISRCTN41544517. www.controlledtrials.com Date last accessed: April 27, 2010.
131. Frith P, ed. *A manual for pulmonary rehabilitation in Australia. Evidence base and standards.* www.lungfoundation.com.au/images/stories/docs/copd/rehab_standards_v3_31_july_2008.pdf
132. McKenzie DK, Frith PA, Burdon JG, *et al.* The COPDX Plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease 2003. *Med J Aust* 2003; 178: Suppl. S7–S39.
133. Lacasse Y, Martin S, Lasserson TJ, *et al.* Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *A Cochrane systematic review.* *Eura Medicophys* 2007; 43: 475–485.
134. Cecins N, Geelhoed E, Jenkins SC. Reduction in hospitalisation following pulmonary rehabilitation in patients with COPD. *Australian Health Review* 2008; 32: 415–422.
135. Bratås O, Espnes G, Rannestad T, *et al.* Pulmonary rehabilitation reduces depression and enhances health-related quality of life in COPD patients – especially in patients with mild or moderate disease. *Chron Respir Dis* 2010; 7: 229–237.
136. Coventry PA, Hind D. Comprehensive pulmonary rehabilitation for anxiety and depression in adults with chronic obstructive pulmonary disease: systematic review and meta-analysis. *J Psychosom Res* 2007; 63: 551–565.
137. Reid WD, Yamabayashi C, Goodridge D, *et al.* Exercise prescription for hospitalized people with chronic obstructive pulmonary disease and comorbidities: a synthesis of systematic reviews. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 297–320.
138. Harrison SL, Greening NJ, Williams JE, *et al.* Have we underestimated the efficacy of pulmonary rehabilitation in improving mood? *Respir Med* 2012; 106: 838–844.
139. Coventry PA. Does pulmonary rehabilitation reduce anxiety and depression in chronic obstructive pulmonary disease? *Curr Opin Pulm Med* 2009; 15: 143–149.
140. Bentsen SB, Wentzel-Larsen T, Henriksen AH, *et al.* Anxiety and depression following pulmonary rehabilitation. *Scand J Caring Sci* 2012 [Epub ahead of print DOI: 10.1111/j.1471-6712.2012.01064.x].
141. Paddison JS, Effing TW, Quinn S, *et al.* Fatigue in COPD: association with functional status and hospitalisations. *Eur Respir J* 2012 [Epub ahead of print DOI: 10.1183/09031936.00021412].

142. Benson H, Beary JF, Carol MP. The relaxation response. *Psychiatry* 1974; 37: 37–46.
143. Mandle CL, Jacobs SC, Arcari PM, *et al.* The efficacy of relaxation response interventions with adult patients: a review of the literature. *J Cardiovasc Nurs* 1996; 10: 4–26.
144. Devine EC, Pearcy J. Meta-analysis of the effects of psychoeducational care in adults with chronic obstructive pulmonary disease. *Patient Educ Couns* 1996; 29: 167–178.
145. American Academy of Hospice and Palliative Medicine, Centre to Advance Palliative Care, Hospice and Palliative Nurses Association, *et al.* National Consensus Project for Quality Palliative Care: Clinical Practice Guidelines for quality palliative care, executive summary. *J Palliat Med* 2004; 7: 611–627.
146. Morrison RS, Meier DE. Clinical practice. Palliative care. *N Engl J Med* 2004; 350: 2582–2590.
147. Aiken LS, Butner J, Lockhart CA, *et al.* Outcome evaluation of a randomized trial of the PhoenixCare intervention: program of case management and coordinated care for the seriously chronically ill. *J Palliat Med* 2006; 9: 111–126.
148. Bourbeau J, Julien M, Maltais F, *et al.* Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003; 163: 585–591.
149. Jonker AA, Comijs HC, Knipscheer KC, *et al.* Promotion of self-management in vulnerable older people: a narrative literature review of outcomes of the Chronic Disease Self-Management Program (CDSMP). *Eur J Ageing* 2009; 6: 303–314.
150. Lorig KR, Sobel DS, Ritter PL, *et al.* Effect of a self-management program on patients with chronic disease. *Eff Clin Pract* 2001; 4: 256–262.
151. Lamers F, Jonkers CC, Bosma H, *et al.* A minimal psychological intervention in chronically ill elderly patients with depression: a randomized trial. *Psychother Psychosom* 2010; 79: 217–226.
152. Effing T, Monninkhof EM, van der Valk PD, *et al.* Self-management education for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007; 4: CD002990.
153. Effing T, Kerstjens H, van der Valk P, *et al.* (Cost)-effectiveness of self-treatment of exacerbations on the severity of exacerbations in patients with COPD: the COPE II study. *Thorax* 2009; 64: 956–962.
154. Cockcroft A, Bagnall P, Heslop A, *et al.* Controlled trial of respiratory health worker visiting patients with chronic respiratory disability. *Br Med J (Clin ResEd)* 1987; 294: 225–228.

Chapter 12

Managing skeletal muscle dysfunction in COPD



Thierry Troosters^{*#}, Wim Janssens^{*} and Marc Decramer^{*}

SUMMARY: Skeletal muscle dysfunction is an important and independent predictor of morbidity and mortality in patients with chronic disease, including COPD. Management of skeletal muscle abnormalities starts with their detection in clinical practice. This can be performed relatively easily using maximum voluntary strength and/or endurance testing. Other techniques exist for the research setting. Prevention of skeletal muscle dysfunction starts in early disease by maintaining weight-bearing physical activity. Once skeletal muscle dysfunction is present, exercise training is the most effective way towards restoration. Pharmacotherapy is in its infancy and for most pharmacological interventions that may potentially enhance muscle function, it has been shown that they work only (or better) when administered in conjunction with an exercise stimulus. Depending on the action of the drug, such programmes may be geared towards resistance or endurance training. Large studies on pharmacological interventions in patients with muscle dysfunction and COPD are, unfortunately, still missing.

KEYWORDS: COPD, exercise, physical activity, rehabilitation, skeletal muscle

^{*}Respiratory Rehabilitation and Respiratory Division, University Hospital Leuven, and
[#]Faculty of Kinesiology and Rehabilitation Sciences, Dept of Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium.

Correspondence: T. Troosters, Respiratory Rehabilitation and Respiratory Division, UZ Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.
Email: Thierry.Troosters@med.kuleuven.be

Eur Respir Monogr 2013; 59: 164–173.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10012212
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Skeletal muscle function is reported to be abnormal in patients with COPD. In patients referred for pulmonary rehabilitation, around 70% of patients present with abnormal skeletal muscle strength. Muscle weakness may be less prevalent in community-based samples (30%) [1] and in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I (~25%) [2]. Abnormalities have been observed at the level of function (muscle size, muscle strength and endurance), and at microscopic (fibre cross-sectional area and fibre type), bioenergetic, and metabolic and molecular biological levels. Clinically reduced skeletal muscle strength, endurance and fatigability contribute to reduced exercise tolerance, the sensation of fatigue and reduced functional performance. At the basis of these clinical features lie a number of alterations, which include altered quadriceps fibre type proportions, innervations, contractility, vascularisation, metabolism and respiration, and susceptibility to contraction induced damage. It is beyond the scope of the present chapter to comprehensively review all mechanisms potentially associated with

skeletal muscle dysfunction. One of the main drivers seems to be long-term physical inactivity, which is characteristic of COPD and occurs in many patients early in disease progression. Several studies reported measurable physical inactivity in patients as early as in GOLD stage I. In these patients, a recent study found that quadriceps weakness was associated with low physical activity levels [2]. In other studies, reduced time spent performing weight-bearing activities was linked to skeletal muscle weakness [3]. On top of the physical inactivity, other COPD-specific factors may contribute to skeletal muscle dysfunction. These factors are the occurrence of exacerbations of the disease, hypoxaemia, the administration of repeated bursts of corticosteroid therapy, malnutrition and hypogonadism in male patients. Whether systemic inflammation and systemic oxidative stress contribute importantly to the development of skeletal muscle dysfunction is not yet fully elucidated. No studies have been performed in which, for example, the impact of systemic inflammation was investigated while correcting for other confounders, such as physical inactivity. One study suggested oxidative stress as a factor contributing to poor skeletal muscle endurance. In that study, the administration of an antioxidant did enhance skeletal muscle endurance. Interestingly, smoking can affect skeletal muscle function directly [4]. In particular, skeletal muscle endurance seems to be affected by smoking. Smoking cessation was associated with an increase in fat-free mass (FFM) [5], but it is, as of yet, unclear whether there is a positive effect of smoking cessation on skeletal muscle strength, after correcting for body weight gain (a known consequence of smoking cessation and a factor known to be associated with increases in muscle strength).

Knowledge of the factors contributing to the aetiology of skeletal muscle dysfunction in individual patients is important to guide the management. In the prevention of skeletal muscle dysfunction, it is clear that maintaining physical activity levels, including weight-bearing activities, is of key importance. Once patients develop muscle weakness it becomes difficult, if not impossible, to enhance skeletal muscle function without introducing formal, high-intensity muscle stimulation, which is achieved with exercise training.

Assessment in clinical practice

At the basis of proper management of skeletal muscle weakness lies the assessment of skeletal muscle function. In clinical practice, this is easily done by the assessment of strength and endurance during maximum voluntary manoeuvres. In patients with COPD, quadriceps strength is often measured using an isometric voluntary muscle contraction. Technical aspects of the assessment of volitional muscle force are reported in detail elsewhere [6]. Since skeletal muscle strength can vary in individual patients from very low to supranormal, techniques to assess skeletal muscle strength need to be able to deal with a large range of force development. The most frequently used techniques are the use of a strain gauge, the use of an isokinetic dynamometer, a hydraulic system or handheld dynamometry. In all cases, it is important to relate the measured values to expected predicted normal values, which vary with age, sex and, for weight-bearing muscles, body weight. As can be appreciated in figure 1a, quadriceps force is poorly related to lung function. Therefore, quadriceps force should be measured separately. FFM is often used as a surrogate measure for skeletal muscle weakness. Figure 1b, however, illustrates the poor relationship between FFM as measured by bioelectrical impedance and quadriceps strength. As can be appreciated, FFM is neither sensitive nor specific enough to define skeletal muscle dysfunction, although patients with low FFM are very likely to present with skeletal muscle dysfunction.

Nonvolitional techniques exist to assess skeletal muscle strength. This is done by measuring the force output upon supramaximal electrical or magnetic stimulation of a superficial motor nerve. Although this technique has the theoretical advantage of not being effort dependent, the assessment is less comfortable for the patient, is more time consuming and requires expensive equipment. In addition, in patients referred for pulmonary rehabilitation, we found excellent correlations between nonvolitional (potentiated twitch) quadriceps strength and the patients' maximal volitional muscle strength (fig. 2).

Besides skeletal muscle strength, local muscle endurance can be assessed. In all studies that investigated muscle strength and local muscle endurance in COPD and controls, the latter was more

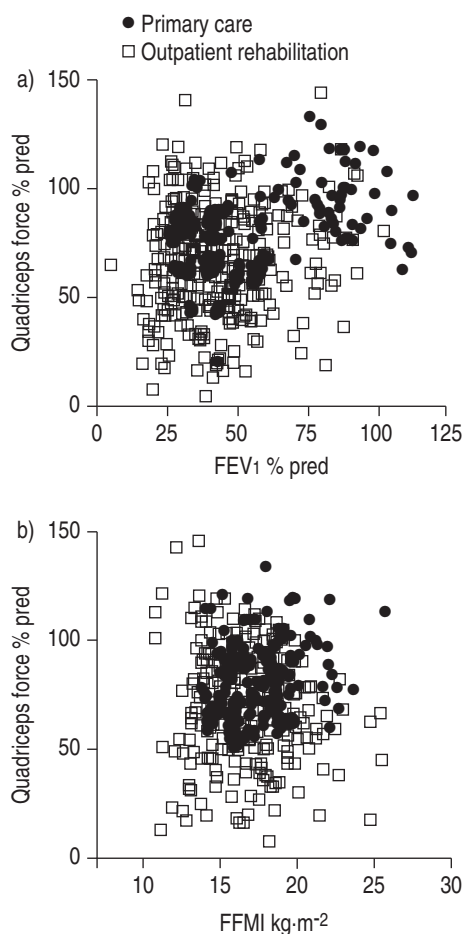


Figure 1. Relationship between a) forced expiratory volume in 1 second (FEV₁) and b) fat-free mass index (FFMI), and quadriceps force expressed in a cohort of patients recruited from primary care and patients referred to our outpatient rehabilitation programme (n=432; mean $\pm$ SD FEV₁ 47 $\pm$ 22% predicted, quadriceps force 73 $\pm$ 29% pred).

skeletal muscle endurance or fatigability, treatment is imperative. The first-line treatment of skeletal muscle dysfunction is exercise training. Specific exercises to target the peripheral muscle may be used to make programmes as effective as possible. In the next few paragraphs, interventions that enhance skeletal muscle function as well as preventive measures are briefly discussed.

Preventing decline in skeletal muscle function

In patients with moderate-to-severe COPD, skeletal muscle strength declines faster than expected by ageing. In a group of 43 COPD patients followed up for mean $\pm$ SD 5.2 $\pm$ 2.1 years and 20 age-matched control subjects, we noticed that quadriceps force declined by 10 $\pm$ 10 N·m·year⁻¹ whereas decline over 8 years was 3 $\pm$ 3 N·m·year⁻¹ in healthy controls *versus* COPD patients ($p < 0.006$; unpublished observations). The main driver of decline was the number of hospital admissions in COPD patients.

Prevention and fast and aggressive treatment of exacerbations, whereby even during exacerbations the skeletal muscle is stimulated appropriately, is an efficient way to prevent decline in skeletal muscle strength associated with severe exacerbations. Exercise training immediately after

affected than the former. Local muscle endurance is probably affected by skeletal muscle atrophy and by oxygen delivery impairments to the peripheral muscle [8]. Hence, it is no surprise that it is more affected than pure muscle strength. Local muscle endurance is an outcome measure that is particularly sensitive to change after exercise training. An important problem with this measure is that, to the best of our knowledge, predicted normal values do not exist and the measure can only be used for within-patient comparison or to characterise groups of patients compared to matched controls.

When more detailed assessment of the skeletal muscle properties is required, a skeletal muscle biopsy can be performed. As the technique is relatively invasive, this is reserved for patients with a suspected neurological problems or myopathy, or for patients participating in mechanistic research projects. Classically, skeletal muscle biopsies may render unique information on skeletal muscle fibre size and type, vascularisation, metabolic enzyme capacity, muscle metabolisms, anabolic or catabolic markers, and/or markers of mitochondrial function.

Managing muscle dysfunction

The effects of enhancing skeletal muscle function in the elderly population are summarised by the American College of Sports Medicine as follows: higher levels of muscular strength are associated with significantly better cardiometabolic risk factor profiles, lower risk of all-cause mortality, fewer cardiovascular disease events, lower risk of developing functional limitations and nonfatal disease [9]. There are no large interventional studies in COPD confirming these claims but there is also no reason why these claims would not apply to the elderly COPD patient. When patients with COPD are diagnosed with skeletal muscle weakness, reduced

exacerbations may also reverse part of the exacerbation-induced reductions in skeletal muscle strength. Furthermore, the use of corticosteroids should be avoided or, as a minimum, skeletal muscle strength should be followed carefully in patients who are administered repeated doses of oral corticosteroids. When muscle force declines, the use of oral corticosteroids should be avoided as much as possible.

In stable patients, the maintenance of physical activity at appropriate levels is crucial. Guidance on healthy physical activity levels is available for the elderly and patients with chronic disease. It should be recommended to introduce some resistance training in the daily routine 2–3 days per week [9]. This can be introduced “physiologically” by promoting stair climbing or rising from a chair. In addition, exercises with elastic bands or weights can be used to maintain skeletal muscle function.

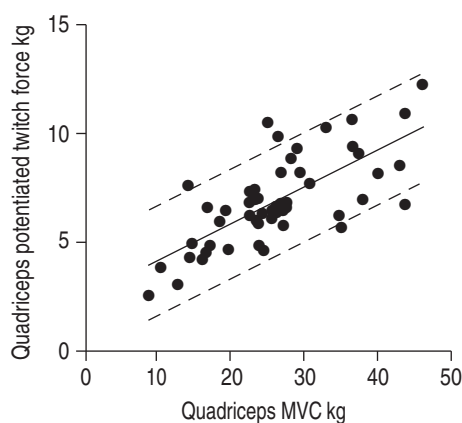


Figure 2. Relationship between quadriceps maximal voluntary contraction (MVC) and quadriceps potentiated twitch force. $r=0.72$, $p<0.0001$. Data from [7].

Whole-body exercise training

Whole-body exercises prescribed as cycling or walking do enhance skeletal muscle aerobic properties. Research in the 1990s convincingly showed that patients who followed high-intensity cycling exercise training increased their anaerobic threshold and oxidative enzyme capacity [10]. Furthermore, fatigability of the peripheral muscle was improved [11]. More recently, studies have shown that specific skeletal muscle growth and differentiation factors were upregulated following exercise training [12, 13]. Similarly, mitochondrial respiration is enhanced following exercise training [14]. In order to be effective in enhancing skeletal muscle function, exercise training needs to be individualised to patients and should take their exercise limitations into account. The training programme itself needs to achieve a stimulus of the muscle that results in “overload”, leading to an anabolic training response [7]. The format of exercise training programmes is extensively described in the American Thoracic Society/European Respiratory Society guidance on pulmonary rehabilitation [15]. Some studies have issued warnings for enhanced oxidative stress in underweight patients [16, 17] but altogether, studies show abundant benefits of exercise training on the peripheral muscle. Whether the skeletal muscle of COPD patients responds as well to an exercise stimulus as the skeletal muscle of healthy age-matched patients has not been fully studied. A recent study suggests that capillary growth was blunted in patients, leading to a slower increase in oxidative capacity in COPD patients with exercise training [18]. Further studies are surely required to investigate whether pharmacological support can be offered to enhance skeletal muscle-induced skeletal muscle growth with whole-body exercise training. It has been known for some time now that the angiotensin converting enzyme (*ACE*) genotype is associated with endurance (insertion allele) or strength (deletion allele) performance in subjects and patients [19]. In the absence of formal randomised controlled trials (RCTs), the effect of ACE inhibitors on training effects in COPD remains a tempting hypothesis for further testing [20, 21].

Specific skeletal muscle resistance training

General effects

Weightlifting exercises (specific muscle resistance training) is a form of exercise training that loads specific skeletal muscles. In patients with COPD, this form of exercise has the additional advantage of a low ventilatory requirement, which allows loading of specific muscles with large absolute loads. This is otherwise difficult with whole-body exercise in severely ventilatory-limited patients.

Resistance training is achieved by lifting weights and is best carried out using resistance training apparatus that control the weight and the range of motion. Typically, relatively few repetitions (e.g. eight repetitions) are used at relatively high loads (e.g. 70% of the weight that can maximally be lifted by the patient). In general, three sets of eight repetitions are used as effective therapy. Several muscle groups can be trained during one session. General recommendations for setting up and progressing resistance training are available [22].

The effects of resistance training on skeletal muscle strength in COPD are well studied [23]. The addition of resistance training to conventional whole-body exercise training does result in more enhanced skeletal muscle strength [24–26]. At a molecular level, the effect of resistance training was recently studied by MENON *et al.* [27]. They reported that resistance training activates satellite cells (although *p*-values just failed to reach significance; *p*=0.07), which are essential for muscle growth. The inflammatory markers increased with resistance training but the increase was comparable to that observed in healthy age-matched subjects. 10 weeks of resistance training tended to increase fibre cross-sectional area of type I, IIa and IIx fibres, although the changes did not reach significance [28]. In this study, myosin heavy chain 2a mRNA was increased and so was insulin-like growth factor 1, an anabolic marker.

An important remark in the context of managing skeletal muscle dysfunction is that the effects of resistance training do wear off once the programme is interrupted [29]. Therefore, it is important to establish a maintenance programme of resistance training to maintain skeletal muscle strength and function [9].

Specific application in patients with exacerbations

As mentioned before, the application of resistance training has specific value in the prevention and treatment of the skeletal muscle dysfunction, which is seen during and immediately following acute exacerbations of COPD. Our group showed that by introducing resistance training during a hospital admission, the muscle catabolic pathways could be effectively blocked and muscle weakness was prevented [30].

Other forms of muscle stimulation

Neuromuscular electrical stimulation and magnetic stimulation

Besides muscle stimulation through physiological muscle activation, other forms of muscle stimulation exist. Neuromuscular electrical stimulation (NMES) is a form of transcutaneous, electrical stimulation of the skeletal muscle fibres. The current is low voltage and is delivered through low-cost devices that allow modulation of the current. Stimulus frequency can vary, but in COPD studies is maintained relatively high (50 Hz) with a pulse duration of 200–400 ms. The duty cycle can be varied but should allow for enough rest between two contractions. Several studies have now investigated the effect of NMES on clinical outcomes and muscle anabolism. Recently, a meta-analysis also confirmed the benefits of NMES in COPD patients [31]. Despite the reported clinical benefits, one recent study was unable to report a clear increase in muscle cross-sectional area with NMES, or changes in aerobic or anaerobic muscle enzymes [32]. The muscle catabolic regulatory factor atrogin was downregulated significantly in patients who were treated with NMES. There seems to be a dose–response relationship between the intensity of the delivered current and the training effects [32, 33]. This limits the use of NMES in patients who are experiencing pain upon stimulation, precluding an appropriate increase in the stimulation current. A clear advantage of the technique is that this form of training does not require the cooperation of the patient and does not load the ventilatory system. Therefore, NMES can be applied in the most severe patients or even during exacerbations [33, 34]. In the context of exacerbations, NMES seemed to be able to block decline in muscle strength [33] (as observed with resistance training) and led to an increase in the proportion of type I fibres [34]. Since the muscle contractions are evoked by external stimulation, they will not

enhance the movement efficiency and, in order to be maximally effective, integration of NMES into a regular training programme may be desired.

Whole-body vibration

Whole-body vibration (WBV) is a relatively new modality of muscle stimulation. In this exercise modality, patients carry out resistance training exercises on a vibrating surface. WBV stimulates muscle contraction by eliciting a reflex contraction upon the vibration-induced muscle shortening. WBV has been shown to be an alternative to conventional training in the healthy elderly. Recently, the modality of training was also applied in patients with COPD [35]. The study showed interesting effects on functional exercise tests favouring the WBV group. Clearly, more research is needed, but given the potential benefits of WBV on bone mineral density and postural control, such studies may be worthwhile in COPD.

Pharmacological anabolic stimulants

Muscle weakness and particularly loss of lean muscle mass can be a target for pharmacotherapy (a recent eloquent review is available by STEINER *et al.* [36]) or pharmacotherapy in combination with exercise training. Depending on the type of anabolic stimulant, the appropriate training programme may differ. When a stimulant enhances skeletal muscle cross-sectional area, resistance training may be most appropriate, whereas endurance training may be more appropriate when oxidative pathways are targeted. Some drugs may also protect the muscle from inappropriate damage induced by “overtraining”. Altogether, little is known regarding pharmacological aids to exercise training and more studies are needed to give clear guidance; clearly, this is an area for developing personalised medicine based on appropriate diagnosis and patient selection.

Stimulating anabolism and muscle function

Clearly, a first measure is to ensure that patients have sufficient caloric intake and, in particular, protein uptake is adequate [37]. The Recommended Dietary Allowance for protein intake is $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. These recommended levels may not be sufficient for patients with a negative protein balance. Specific attention to nutrition may be beneficial, particularly in the approximately 30% of outpatients who are “nutritionally at risk” (unintentional weight or appetite loss) [38].

Anabolic steroids (*e.g.* testosterone) are probably the most widely studied anabolic stimulant. Hypogonadism (*i.e.* low androgen levels) is associated with muscle weakness [39] and testosterone promotes muscle growth [40], particularly when combined with resistance training. For some patients, the increase in haematocrit, observed in testosterone supplementation [41], is of additional benefit. One study showed clear benefits in terms of muscle strength gain when testosterone was combined with resistance training in hypogonadal males [42]. The trial suggests that testosterone could be used in this subpopulation of patients to help restore muscle strength and muscle mass.

Growth hormone supplementation has been used to increase athletic performance [43] but administration of growth hormone in patients with COPD has not shown significant effects on peripheral muscle function [44]. The use of growth hormone release factors is a new avenue for interventions but proper RCTs in COPD have not yet been performed. The only substance of this category, ghrelin, did result in benefits in functional exercise tolerance and symptoms, but effects on the peripheral muscle were not studied [45].

Antioxidant administration may also have potential value in patients with COPD. Administration of *N*-acetylcysteine in high doses acutely enhanced skeletal muscle endurance [46]. No studies have taken this forward successfully in an exercise training study. Since, in particular, cachectic patients may experience difficulties in replenishing their antioxidant stores after exercise training [17], they may be a potential target group. Recently, pressurised whey protein has been used as an antioxidant nutritional supplement. This small study suggests that whey protein administration, in

combination with endurance training, has beneficial effects on enhancing endurance exercise capacity in COPD [47].

Another nutritional supplement that received some attention in COPD is creatine. Creatine can be taken up by skeletal muscle as a substrate to promote explosive muscle work. Unfortunately, the use of creatine supplements in COPD has led to largely negative study results [48, 49]. Since high doses of creatine supplements can lead to renal dysfunction, the use of these supplements should not be advised.

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that regulate genes involved in the energy homeostasis. PPARs also inhibit inflammatory responses and the related muscle wasting upon inflammation. In patients with COPD, in particular in cachectic COPD patients, PPAR- α is under-expressed, compared with controls, in the skeletal muscle [50]. PPARs can be activated by a number of synthetic and endogenous ligands, including ω -3 polyunsaturated fatty acids (n-3 PUFAs) present in fish oil. In addition to their potential to activate PPARs, n-3 PUFAs exert pleiotropic actions on the nervous and cardiovascular systems. Fish oil administration has been shown to enhance muscle strength and functional status in elderly females [51]. One study investigated the effect of 8 weeks of treatment with PUFAs in conjunction with rehabilitation and found more improvement in exercise endurance time than with rehabilitation alone. No differences were found, however, for muscle strength in this study. Synthetic ways to activate PPARs are being evaluated. In animal studies of arthritis treatment, PPAR- α antagonists did prevent arthritis-induced skeletal muscle wasting [52]. This may prove to be an interesting avenue for COPD, in particular during periods of acute wasting, such as during exacerbations. PPAR- δ agonists are also being tested and have probably found their way already to the sports milieu. As an example, 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside (AICAR), a PPAR- δ -AMP kinase agonist, was recently placed by the World Anti-Doping Agency on its list of hormone and metabolic modulators [53]. These drugs, in combination with aerobic training, may increase fatigue, the proportion of resistant type I muscle fibres, mitochondrial biogenesis, angiogenesis and insulin sensitivity, ultimately enhancing physical performance [53]. Importantly, most effects of AICAR are seen when combined with an aerobic exercise stimulus, stressing the need to integrate future pharmacotherapy with an appropriate mechanical (*i.e.* exercise) stimulus to the skeletal muscle [54]. The effectiveness and safety of these molecules in compromised patients with COPD is, however, yet to be tested.

A last anabolic nutritional supplement that deserves mentioning is vitamin D. Vitamin D is classically associated with its role in the maintenance of bone mineral density. Over the past few years, however, vitamin D supplementation has received attention beyond preservation of bone, including in COPD [55, 56]. Vitamin D and its receptor do play a role in skeletal muscle contractile function. In addition, vitamin D exerts anti-inflammatory properties that may be beneficial in the context of exercise training. In the healthy elderly, muscle strength and endurance was related to 1,25-dihydroxyvitamin D levels, a relationship not confirmed in COPD by these authors [57]. Studies suggest an enhanced skeletal muscle function in subjects supplemented with vitamin D. A recent subanalysis of a larger trial investigating the effects of vitamin D supplements in patients at risk for exacerbations [58] suggested a synergistic effect of vitamin D supplements with exercise training [59]. Supplementing patients with vitamin D may be of particular interest to those patients with COPD suffering from vitamin D deficiency (*i.e.* serum levels <20 ng·mL⁻¹; 60% and 77% of patients in GOLD stage III and IV [60], respectively). In order to exert non-calcaemic effects, the doses of vitamin D supplements may need to be higher than to obtain calcaemic effects. A maximal dose of 4,000 IU per day is considered to be the upper limit of tolerability and safety with regards to hypercalcaemia and kidney stone formation [61]. Clearly, further studies in well-targeted patients are needed.

Inhibition of catabolism and deterioration of muscle function

An even less explored field for pharmacological applications are drugs that could block muscle wasting in moments where acute muscle wasting may be expected. In such situations, catabolic

pathways are upregulated [30] and these could be blocked. A potentially interesting pathway may be blockade of the ubiquitin proteasome pathway [62] or the myostatin pathway. The latter is upregulated when muscle wasting occurs. Myostatin inhibition through antibodies is possible [63] but so far has not been used in patients with COPD at risk of muscle wasting (e.g. during exacerbations).

Conclusion

Managing skeletal muscle dysfunction starts with proper clinical assessment of skeletal muscle strength. This can be performed in clinical routine using maximal voluntary contractions. There is less consensus and an absence of predicted normal values for the assessment of skeletal muscle endurance. When muscle weakness is observed, exercise training is the most studied intervention to enhance and potentially normalise skeletal muscle function. Pharmacotherapy has only scantily been studied but there is certainly a future in combining specific pharmacological and non-pharmacological interventions in well-selected patients and with proper timing.

Support Statement

The authors were supported by the following grants: FWO-Vlaanderen G.0687.09, G.0674.09 and G087113N, and OT111088.

Statement of Interest

M. Decramer has been part of advisory boards for Boehringer, Pfizer, GSK, Nycomed and Altana. He has performed consulting work for Boehringer, Pfizer and GSK. He also received lecture fees from these companies. All of the above amounted to less than €10,000 *per annum*. He received a research grant of €45,000 *per annum* from AstraZeneca.

References

1. van Wetering CR, van Nooten FE, Mol SJ, *et al.* Systemic impairment in relation to disease burden in patients with moderate COPD eligible for a lifestyle program. Findings from the INTERCOM trial. *Int J Chron Obstruct Pulmon Dis* 2008; 3: 443–451.
2. Shrikishna D, Patel M, Tanner RJ, *et al.* Quadriceps wasting and physical inactivity in patients with COPD. *Eur Respir J* 2012; 40: 1115–1122.
3. Pitta F, Troosters T, Spruit MA, *et al.* Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 972–977.
4. Wust RC, Morse CI, de Haan, *et al.* Skeletal muscle properties and fatigue resistance in relation to smoking history. *Eur J Appl Physiol* 2008; 104: 103–110.
5. Hopkinson NS, Tennant RC, Dayer MJ, *et al.* A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. *Respir Res* 2007; 8: 25.
6. Robles PG, Mathur S, Janaudis-Ferreira T, *et al.* Measurement of peripheral muscle strength in individuals with chronic obstructive pulmonary disease: a systematic review. *J Cardiopulm Rehabil Prev* 2011; 31: 11–24.
7. Burtin C, Saey D, Saglam M, *et al.* Effectiveness of exercise training in patients with COPD: the role of muscle fatigue. *Eur Respir J* 2012; 40: 338–344.
8. Malaguti C, Napolis LM, Villaca D, *et al.* Relationship between peripheral muscle structure and function in patients with chronic obstructive pulmonary disease with different nutritional status. *J Strength Cond Res* 2011; 25: 1795–1803.
9. Garber CE, Blissmer B, Deschenes MR, *et al.* American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011; 43: 1334–1359.
10. Troosters T, Casaburi R, Gosselink R, *et al.* Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 19–38.
11. Mador MJ, Kufel TJ, Pineda LA, *et al.* Effect of pulmonary rehabilitation on quadriceps fatigability during exercise. *Am J Respir Crit Care Med* 2001; 163: 930–935.
12. Vogiatzis I, Stratakos G, Simoes DC, *et al.* Effects of rehabilitative exercise on peripheral muscle TNF- α , IL-6, IGF-I and MyoD expression in patients with COPD. *Thorax* 2007; 62: 950–956.
13. Vogiatzis I, Terzis G, Stratakos G, *et al.* Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* 2011; 140: 744–752.

14. Brønstad E, Rognmo O, Erik TA, *et al.* High-intensity knee extensor training restores skeletal muscle function in COPD patients. *Eur Respir J* 2012; 40: 1130–1136.
15. Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.
16. Rabinovich RA, Mayer AM, Ardite E, *et al.* Skeletal muscle redox capacity is reduced in COPD patients with low BMI. *Am J Respir Crit Care Med* 2003; 167: A73.
17. Rabinovich RA, Ardite E, Mayer AM, *et al.* Training depletes muscle glutathione in patients with chronic obstructive pulmonary disease and low body mass index. *Respiration* 2006; 73: 757–761.
18. Gouzi F, Prefaut C, Abdellaoui A, *et al.* Blunted muscle angiogenic training-response in COPD patients *versus* sedentary controls. *Eur Respir J* 2012 [Epub ahead of print DOI: 10.1183/09031936.00053512].
19. Puthuchear Z, Skipworth JR, Rawal J, *et al.* The ACE gene and human performance: 12 years on. *Sports Med* 2011; 41: 433–448.
20. Wang P, Fedoruk MN, Rupert JL. Keeping pace with ACE: are ACE inhibitors and angiotensin II type 1 receptor antagonists potential doping agents? *Sports Med* 2008; 38: 1065–1079.
21. Shrikrishna D, Astin R, Kemp PR, *et al.* Renin–angiotensin system blockade: a novel therapeutic approach in chronic obstructive pulmonary disease. *Clin Sci (Lond)* 2012; 123: 487–498.
22. American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009; 41: 687–708.
23. O'Shea SD, Taylor NF, Paratz J. Peripheral muscle strength training in COPD: a systematic review. *Chest* 2004; 126: 903–914.
24. Dourado VZ, Tanni SE, Antunes LC, *et al.* Effect of three exercise programs on patients with chronic obstructive pulmonary disease. *Braz J Med Biol Res* 2009; 42: 263–271.
25. Ortega F, Toral J, Cejudo P, *et al.* Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 669–674.
26. Vonbank K, Strasser B, Mondrzyk J, *et al.* Strength training increases maximum working capacity in patients with COPD – randomized clinical trial comparing three training modalities. *Respir Med* 2012; 106: 557–563.
27. Menon MK, Houchen L, Singh SJ, *et al.* Inflammatory and satellite cells in the quadriceps of patients with COPD and the response to resistance training. *Chest* 2012; 142: 1134–1142.
28. Lewis MI, Fournier M, Storer TW, *et al.* Skeletal muscle adaptations to testosterone and resistance training in men with COPD. *J Appl Physiol* 2007; 103: 1299–1310.
29. Houchen L, Steiner MC, Singh SJ. How sustainable is strength training in chronic obstructive pulmonary disease? *Physiotherapy* 2009; 95: 1–7.
30. Troosters T, Probst VS, Crul T, *et al.* Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 181: 1072–1077.
31. Sillen MJ, Speksnijder CM, Eterman RM, *et al.* Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest* 2009; 136: 44–61.
32. Vivodtzev I, Debigare R, Gagnon P, *et al.* Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. *Chest* 2012; 141: 716–725.
33. Giavedoni S, Deans A, McCaughey P, *et al.* Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. *Respir Med* 2012; 106: 1429–1434.
34. Abdellaoui A, Prefaut C, Gouzi F, *et al.* Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. *Eur Respir J* 2011; 38: 781–788.
35. Gloeckl R, Heinzlmann I, Baeuerle S, *et al.* Effects of whole body vibration in patients with chronic obstructive pulmonary disease – a randomized controlled trial. *Respir Med* 2012; 106: 75–83.
36. Steiner MC, Roubenoff R, Tal-Singer R, *et al.* Prospects for the development of effective pharmacotherapy targeted at the skeletal muscles in chronic obstructive pulmonary disease: a translational review. *Thorax* 2012; 67: 1102–1109.
37. Evans WJ. Protein nutrition, exercise and aging. *J Am Coll Nutr* 2004; 23: Suppl., 601S–609S.
38. Weekes CE, Emery PW, Elia M. Dietary counselling and food fortification in stable COPD: a randomised trial. *Thorax* 2009; 64: 326–331.
39. van Vliets M, Spruijt MA, Verleden G, *et al.* Hypogonadism, quadriceps weakness, and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 1105–1111.
40. Bhasin S, Storer TW, Berman N, *et al.* Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J Clin Endocrinol Metab* 1997; 82: 407–413.
41. Creutzberg EC, Wouters EF, Mostert R, *et al.* A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest* 2003; 124: 1733–1742.
42. Casaburi R, Bhasin S, Cosentino L, *et al.* Anabolic effects of testosterone replacement and strength training in men with COPD. *Am J Respir Crit Care Med* 2004; 170: 870–878.
43. Baumann GP. Growth hormone doping in sports: a critical review of use and detection strategies. *Endocr Rev* 2012; 33: 155–186.
44. Burdet L, de Muralt B, Schutz Y, *et al.* Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. *Am J Respir Crit Care Med* 1997; 156: 1800–1806.

45. Miki K, Maekura R, Nagaya N, *et al.* Ghrelin treatment of cachectic patients with chronic obstructive pulmonary disease: a multicenter, randomized, double-blind, placebo-controlled trial. *PLoS One* 2012; 7: e35708.
46. Koehlin C, Couillard A, Simar D, *et al.* Does oxidative stress alter quadriceps endurance in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2004; 169: 1022–1027.
47. Laviolette L, Lands LC, Daultbaev N, *et al.* Combined effect of dietary supplementation with pressurized whey and exercise training in chronic obstructive pulmonary disease: a randomized, controlled, double-blind pilot study. *J Med Food* 2010; 13: 589–598.
48. Al-Ghimlas F, Todd DC. Creatine supplementation for patients with COPD receiving pulmonary rehabilitation: a systematic review and meta-analysis. *Respirology* 2010; 15: 785–795.
49. Deacon SJ, Vincent EE, Greenhaff PL, *et al.* Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 178: 233–239.
50. Remels AH, Schrauwen P, Broekhuizen R, *et al.* Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. *Eur Respir J* 2007; 30: 245–252.
51. Rodacki CL, Rodacki AL, Pereira G, *et al.* Fish-oil supplementation enhances the effects of strength training in elderly women. *Am J Clin Nutr* 2012; 95: 428–436.
52. Castellero E, Nieto-Bona MP, Fernandez-Galaz C, *et al.* Fenofibrate, a PPAR α agonist, decreases atrogenes and myostatin expression and improves arthritis-induced skeletal muscle atrophy. *Am J Physiol Endocrinol Metab* 2011; 300: E790–E799.
53. Sanchis-Gomar F, Lippi G. Telmisartan as metabolic modulator: a new perspective in sports doping? *J Strength Cond Res* 2012; 26: 608–610.
54. Goodyear LJ. The exercise pill – too good to be true? *N Engl J Med* 2008; 359: 1842–1844.
55. Janssens W, Lehouck A, Carremans C, *et al.* Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. *Am J Respir Crit Care Med* 2009; 179: 630–636.
56. Janssens W, Mathieu C, Boonen S, *et al.* Vitamin D deficiency and chronic obstructive pulmonary disease: a vicious circle. *Vitam Horm* 2011; 86: 379–399.
57. Jackson AS, Shrikrishna D, Kelly JL, *et al.* Vitamin D and skeletal muscle strength and endurance in COPD. *Eur Respir J* 2013; 41: 309–316.
58. Lehouck A, Mathieu C, Carremans C, *et al.* High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2012; 156: 105–114.
59. Hornikx M, Van Remoortel H, Lehouck A, *et al.* Vitamin D supplementation during rehabilitation in COPD: a secondary analysis of randomized data. *Respir Res* 2012; 13: 84.
60. Janssens W, Bouillon R, Claes B, *et al.* Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* 2010; 65: 215–220.
61. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D (2011 revision). Institute of Medicine. Washington, National Academies Press, 2011.
62. Caron AZ, Haroun S, Leblanc E, *et al.* The proteasome inhibitor MG132 reduces immobilization-induced skeletal muscle atrophy in mice. *BMC Musculoskelet Disord* 2011; 12: 185.
63. Wagner KR, Fleckenstein JL, Amato AA, *et al.* A phase I/II trial of MYO-029 in adult subjects with muscular dystrophy. *Ann Neurol* 2008; 63: 561–571.

Chapter 13

Lung cancer in COPD

Georgia Hardavella and Stephen Spiro



SUMMARY: COPD and lung cancer are the commonest burdens to many health services throughout the world and, as a consequence, much has been learnt of their interdependence, epidemiology and optimal management. COPD and lung cancer are strongly associated and coexist in a large number of patients. Smoking is still a major public health issue and remains the causal factor for the majority of cases of COPD and lung cancer. Treating lung cancer patients with severe COPD is a clinical challenge for thoracic physicians and warrants a multidisciplinary team approach. In this chapter, we discuss the epidemiological overlap of those two diseases, address the special features of patient management when these two conditions coexist and consider the common underlying link between them.

KEYWORDS: COPD, eligibility criteria, lung cancer, surgical tolerance

Dept of Thoracic Medicine,
University College Hospital, London,
UK.

Correspondence: S. Spiro, 66 Grange
Gardens, Pinner, Middlesex, HA5
5QF, UK.
Email: stephenspiro@btinternet.com

Eur Respir Monogr 2013; 59: 174–188.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10012312
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Epidemiology

Lung cancer has become one of the world's leading causes of preventable death [1, 2]. Undoubtedly, it is the leading cause of cancer deaths worldwide in both males and females (1.4 million deaths per year) and it accounts for approximately 20% of all cancer deaths in Europe [3]. Males are more frequently affected worldwide (1.1 million cases), with the highest rates in Central, Eastern and Southern Europe, North America and East Asia [4].

In 2008, there were an estimated 1.61 million new cases worldwide, representing 12.7% of all new cancers. 55% of cases occurred in developing countries. Even though an extensive list of risk factors has been well characterised and lifestyle changes have occurred around tobacco consumption, particularly in males in Western Europe, it remains a huge health problem [5], with tobacco consumption being the main driver.

In Europe, the overall 5-year survival rate in patients with lung cancer remains poor at 11.2% for males and 13.9% for females [5]. The overall 5-year survival for 2001–2007 in the USA was 15.6% [6].

COPD is also a major public health issue and the fourth leading cause of death in the world [7, 8]. The COPD burden is expected to increase in coming decades due to ageing of the population and ongoing exposure to tobacco and other risk factors [9].

The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) investigated the epidemiology of COPD in five major Latin American cities. The COPD rates ranged from 7.8% in Mexico City, Mexico to 19.7% in Montevideo, Uruguay [10].

A systematic review and meta-analysis of studies carried out in 28 countries worldwide (in the Americas, Europe, South Africa, South East Asia, the West Pacific and the Eastern Mediterranean) during 1998–2004 [11] and a Japanese study [12] showed that COPD prevalence is significantly higher in smokers, males and urban residents.

Prevalence of lung cancer in patients with COPD

Tobacco smoking continues to be the main risk factor for both COPD and lung cancer [13]. Several large studies have addressed the risk and incidence of lung cancer in patients with COPD [14–16]. VAN DEN EEDEN and FRIEDMAN [14] studied 171,311 patients and evaluated for the first time the relationship between forced expiratory volume in 1 second (FEV₁) and lung cancer among smokers and never-smokers. Subjects were stratified by FEV₁ into quintiles. FEV₁ was related to lung cancer incidence only in former and current smokers, thus constituting a physiological marker for smoking-induced pulmonary damage. Proportional hazards models in that study revealed a decreasing trend in risk of lung cancer incidence with increasing FEV₁ quintile among former and current smokers. Subjects in the lowest quintile, with FEV₁ ≤ 2.3 L, had a relative risk (RR) of 1.86 for lung cancer compared with subjects in the highest FEV₁ quintile (FEV₁ ≥ 3.9 L) [14]. KULLER *et al.* [15] studied 12,866 patients and their data agreed with that of VAN DEN EEDEN and FRIEDMAN [14], although the RR was higher. In this study [15], the RR for lung cancer between lowest and highest quintile was 3.57 and the authors suggested that FEV₁ may identify smokers at very high risk of lung cancer. In agreement with these data, HOLE *et al.* [16] studied 15,411 subjects prospectively in Scotland, UK and showed that impaired lung function is a major clinical indicator of mortality risk for a wide range of diseases including lung cancer. In males, the lowest quintile for relative FEV₁ (FEV₁ < 73% predicted) showed a relative hazard ratio (HR) for death from lung cancer of 2.53 (95% CI 1.69–2.79, *p* < 0.001) compared with males in the highest FEV₁ quintile. DE TORRES *et al.* [17] reported that lung cancer in patients with COPD has an incidence of 8.5% with a predilection in males *versus* females, which agrees with previously published data [14–16]. A higher incidence (83.8%) is noted in patients aged > 64 years [18].

Several studies have shown that the presence of radiographically proven emphysema is an important independent risk factor for lung cancer in longer term follow-up studies [17, 19–21] in European and American populations.

However, abnormal lung function has drawn conflicting results regarding its association with lung cancer. A systematic review and meta-analysis by WASSWA-KINTU *et al.* [22] reported that lung cancer is more frequently found in patients with a reduced FEV₁, independent of smoking history. Even a relatively modest reduction in FEV₁ is a significant predictor of lung cancer, especially in females [22]. The relationship they reported was severity dependent, *i.e.* the patients with the worst lung function had the highest risk while those with preserved lung function had the lowest risk. MANNINO *et al.* [20] and WILSON *et al.* [21] have also shown that, adjusting for sex, age, years of cigarette smoking and number of smoked cigarettes per day, lung cancer is associated with the presence of airflow obstruction. Contrary to common belief, DE TORRES *et al.* [17] reported that lung cancer incidence density decreased as the severity of airflow obstruction at baseline increased. In this study, the greatest incidence of lung cancer was in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages I (10.2%) and II (9.1%) rather than III (8.7%) and IV (3.9%). DE TORRES *et al.* [18] had previously shown a high incidence of lung cancer in stage I with minimal changes in pulmonary function tests (PFTs) [18]. In their recent study [17], older age, low diffusing capacity of the lung for carbon monoxide (DL_{CO}), GOLD stages I and II, and low body mass index (BMI) were independent risk factors for the development of lung cancer. DL_{CO} seems to be of interest as it is the best physiological marker of computed tomography (CT)-diagnosed emphysema, which has been commonly agreed to be an independent risk factor for the development of lung cancer [17, 23]. Moreover, a strong association between emphysema detected on CT and lung cancer was found even in individuals with normal airway function [17, 24, 25].

The presence of COPD has an additional effect on mortality in patients who contract lung cancer according to data from the UK General Practice Research Database [19]. Mortality rates were 75.17 per 100 person-years in males with lung cancer previously diagnosed with COPD, compared with 39.56 per 100 person-years in patients diagnosed with lung cancer and no COPD [19]. Although the survival of patients diagnosed with lung cancer was low during the first 3 years (26%), survival was much worse among those with known COPD (15%) [19].

Prevalence of COPD in patients with lung cancer

COPD is an independent risk factor that is associated with an increased risk of lung cancer [26] and these two diseases seem to share common susceptibility factors [27]. As described here, the prevalence of COPD in patients with lung cancer has been studied in several observational studies and its prevalence is increased. Sex differences have raised some controversy in the literature regarding COPD and lung cancer separately [22, 28–36]. Data from large epidemiological studies [28–31] support the notion that female smokers have increased susceptibility to COPD. Whether females have increased risk for lung cancer remains controversial [22, 32–36]. A sex effect for COPD prevalence in patients with lung cancer still remains uncertain. LOGANATHAN *et al.* [37] retrospectively reviewed 294 patients with newly diagnosed primary lung cancer who underwent PFTs before receiving any type of cancer therapy. The study showed a significantly lower prevalence of COPD in females diagnosed with lung cancer (52.5%) than in males (72.8%) (OR 0.41, 95% CI 0.25–0.67; $p=0.0003$). Based on this information, the authors suggested that sex-based differences should be taken into account when building up strategies for lung cancer screening. This could, in turn, lead to the assumption that COPD in females is less likely to be associated with lung cancer. However, this was a small study from which to make such a big statement, and larger epidemiological studies are needed in this area. Moreover, those data contradict the recent assumption that females, for largely unknown reasons, appear particularly vulnerable to the adverse effects of cigarette smoking [38]. Animal studies have raised the possibility that females exhibit an increased production of carcinogenic and airway-toxic molecules due to important sex-related differences in the metabolism of some constituents of cigarette smoke. When exposed to smoke, females also appear more vulnerable to DNA damage, are more likely to develop DNA adducts and have decreased capacity for DNA repair [38].

YOUNG *et al.* [39] confirmed the increased prevalence of COPD in patients with lung cancer (50% in 301 lung cancer cases) *versus* community-based smoking controls (8%), as previously shown in worldwide prevalence studies [40]. This increased prevalence of COPD in subjects with lung cancer was independent of sex in contrast to the data reported by LOGANATHAN *et al.* [37]. In addition to the observations in white patients, an increased prevalence of COPD in subjects with lung cancer has also been reported in African–American patients [41]. This is the only study so far to specifically address the prevalence of COPD in African–American patients with lung cancer and it showed a high prevalence of COPD (94% in males and 78% in females). Moreover, 75% of subjects were diagnosed with emphysema based on CT, with or without airflow obstruction. GOLD classification scores did not differ by sex among those with spirometry-diagnosed COPD ($p=0.34$) and there was no significant difference in the risk of death from lung cancer in relation to the presence or absence of COPD [41]. In this context, patients with lung cancer and COPD, diagnosed either *via* spirometry or CT, did not show an increased risk of death compared with patients with lung cancer and no COPD after adjusting for age at diagnosis, sex and stage (HR 1.31, 95% CI 0.68–2.53) [41]. Conversely, GULLÓN *et al.* [23] reported that survival decreased with the presence of emphysema (univariate analysis: $p=0.02$) in 353 subjects from Tenerife, Spain, and identified emphysema (multivariate analysis: HR 1.49, 95% CI 1.11–2.01) as an independent prognostic factor for non-small cell lung cancer (NSCLC) along with a performance status ≥ 2 (HR 2.12, 95% CI 1.31–3.38), surgery (HR 0.3, 95% CI 0.15–0.56) and chemotherapy (HR 0.34, 95% CI 0.31–0.57). Therefore, these authors suggested that emphysema should be considered for prognostic studies on comorbidity. These two contradictory studies [23, 41] address different populations (African–American *versus* Spanish), and this could explain the contrast in findings on the grounds of possible genetic links between patients' race and susceptibility to COPD and lung cancer death risk.

Management of lung cancer in patients with COPD

Management of lung cancer in COPD patients constitutes a common clinical problem as COPD can have major implications for the scope of management of lung cancer; it can affect performance status and fitness for both surgery and radical radiotherapy [42].

PFTs, cardiopulmonary exercise testing and nuclear perfusion lung scanning are recommended for assessing pulmonary risk and patient selection for lung resection [43–45]. Due to coexisting impairments in lung function, patients with COPD often do not meet traditional criteria for tolerance of definitive surgical lung cancer therapy [44].

In clinical practice, the majority of patients with COPD fall outside the safety range of pre-operative values recommended for undergoing lung resection following simple assessment with spirometry alone [44]. While it is important to offer any technically curative subject the option of curative surgery, in someone with the additional burden of COPD, it is essential to assess with more complex physiological measurements whether curative treatment by surgery or possibly radiotherapy is feasible [45, 46, 47]. The responsibility of the treating team is to offer all those who may benefit from curative treatment as safe a prediction of outcome as possible, without erring too far on the side of caution and denying cure on the grounds of inadequate assessment or uncoordinated care.

Table 1 shows the functional criteria determining the acceptable criteria for anatomic surgical resection (segmentectomy, wedge resection, lobectomy, bilobectomy or pneumonectomy) for operable-stage lung cancer.

Lobectomy

Several studies, the majority of which are small, have suggested that COPD can significantly affect the relationship between predicted and actual post-operative changes in pulmonary function [48–58]. Table 2 shows a summary of recent reports (2003–2011) of lung resection in patients with COPD and the impact of FEV1 on 5-year survival [48–58].

Table 1. Criteria for tolerance and intolerance of anatomic surgical resection for operable nonsmall cell lung cancer		
Criterion	Value	Action
Pre-operative FEV1	>1.5 L or >80% pred	Eligible for lobectomy
Pre-operative DL,co	>80% pred	Eligible for lobectomy
ppoFEV1	>40% pred	Eligible for lobectomy
ppoDL,co	>40% pred	Eligible for lobectomy
VO2,max	>15 mL·kg ⁻¹ ·min ⁻¹	Eligible for lobectomy
If lung function inadequate		
Pre-operative FEV1 and DL,co	<80% pred	Calculation of ppo
After calculation of ppo		
ppoFEV1	≥30% pred	Pre-operative exercise testing
ppoDL,co	<40% pred	Pre-operative exercise testing
ppoFEV1 and ppoDL,co	<30% pred	Counselling for nonstandard surgery and for nonsurgical treatment options
VO2,max	<15 mL·kg ⁻¹ ·min ⁻¹	Counselling for nonstandard surgery and for nonsurgical treatment options
Walk	<25 shuttles on 2 shuttle walks or <1 flight of stairs	Counselling for nonstandard surgery and for nonsurgical treatment options
SO2	<90%	Further physiological testing
PcO2	>45 mmHg	Further physiological testing

FEV1: forced expiratory volume in 1 second; DL,co: diffusing capacity of the lung for carbon monoxide; VO2,max: maximal oxygen uptake; ppo: predicted post-operative; SO2: oxygen saturation; PcO2: carbon dioxide tension; % pred: % predicted.

Table 2. Recent reports (2003–2011) of lung cancer resection in COPD patients and the impact on forced expiratory volume in 1 second (FEV₁) and 5-year survival

First author [ref.]	Study type	Study size n	Subjects	TNM stage	Surgery	Mean pre-operative FEV ₁	Post-operative FEV ₁	5-year survival
SEKINE [49]	Retrospective	521	COPD patients (n=48), non-COPD patients (n=473)	I–IV	Lobectomy	COPD group: 1.8 L; non-COPD group: 2.3 L	COPD group: 13.1% reduction from pre-operative value; non-COPD group: 29.2% reduction from pre-operative value	No data
CHOONG [50]	Retrospective	21	Severe emphysema	I–IV	Lobectomy or wedge with or without LVRS in a lobe separate from the tumour	0.70 L (29% pred)	1.0 L (40% pred)	62.7%
BOBBIO [51]	Prospective	11	COPD patients	No data	Lobectomy/bilobectomy	1.4 L (53%)	1.4 L (53% pred)	No data
BALDI [52]	Retrospective multicentre national	137	COPD patients (n=88), non-COPD patients (n=49)	No data	Lobectomy	COPD: 56% pred; non-COPD: 96% pred	COPD: 64% pred; non-COPD: 78% pred	No data
IWASAKI [53]	Retrospective	50	COPD patients	No data	Lobectomy (n=31), segmentectomy (n=11), bilobectomy (n=8)	Among subjects with FEV ₁ ≥50 and <80% pred: 1.53 L; among subjects with FEV ₁ <50% pred: 1.03 L	FEV ₁ decreased more than ppo value	73.9% (no difference between moderate and severe groups)
SUBOTIC [54]	Prospective	82	COPD patients (n=35), non-COPD patients (n=47)	No data	Lobectomy and pneumonectomy	COPD: 1.60 L (lobectomy), 1.91 L (pneumonectomy); non-COPD: 2.85 L (lobectomy), 2.93 L (pneumonectomy)	COPD: 12% reduction from pre-operative value (lobectomy), 18% reduction (pneumonectomy); non-COPD: 25% reduction from pre-operative value (lobectomy), 43% reduction (pneumonectomy)	No data
SCHATTEMBERG [55]	Retrospective	79	COPD patients	No data	Lobectomy	1.2 L	8% reduction from pre-operative value after surgery Values returned to baseline 3 months post-operation	No data

Table 2. Continued.

First author [ref.]	Study type	Study size n	Subjects	TNM stage	Surgery	Mean pre-operative FEV ₁	Post-operative FEV ₁	5-year survival
MARTIN-UCAR [56]	Retrospective	118	Patients with apical heterogeneous emphysema (n=27), control patients (n=91)	I	Lobectomy, lobar LVRS	Lobar LVRS : FEV ₁ 45% pred; lobectomy: FEV ₁ 77% pred	Lobar LVRS patients: ppoFEV ₁ 34% pred; lobectomy patients: ppoFEV ₁ 61% pred	Lobar LVRS patients: 35%; lobectomy patients: 65%
KUSHIBE [57]	Retrospective	100	COPD patients (n=30), non-COPD patients (n=70)	No data	Lobectomy	COPD with FEV ₁ ≥80% pred: 2.09 L; COPD with FEV ₁ <80% pred: 1.37 L; non-COPD group: 2.48 L	COPD with FEV ₁ ≥80% pred: 11.6% reduction from pre-operative value; COPD with FEV ₁ <80% pred: 4.7% increase from pre-operative value; non-COPD group: 14.7% reduction from pre-operative value	No data
LAU [58]	Retrospective	84	Severe pulmonary dysfunction (ppoFEV ₁ ≤40% pred)	I-III	Open segmentectomy, VATS (n=49) (study group) Open thoracotomy/lobectomy (n=35) (control group)	Study group: FEV ₁ 42% pred; control group: FEV ₁ 40% pred	Study group: ppoFEV ₁ 32.7% pred; control group: ppoFEV ₁ 32.8% pred	Follow-up: 39 months; study group: 49%; control group: 40%
PUENTE-MAESTÚ [48]	Prospective cohort	126	Patients with non-small cell bronchogenic carcinoma/resectable metastasis with an FEV ₁ or DL _{CO} <80% pred and no other severe clinical condition precluding surgery (obstructive disease, n=113; restrictive disease, n=13)	I-III	Pneumonectomy, (b)lobectomy, anatomic segmentectomy, VATS wedge resection (surgical group) Radiotherapy, ablation with radiofrequency, chemoradiotherapy, supportive care (nonsurgical group)	Surgical group: FEV ₁ 63% pred; nonsurgical group: FEV ₁ 58% pred	Surgical group: ppoFEV ₁ 44.9% pred; nonsurgical group: ppoFEV ₁ 41% pred	Available data for 2-year survival: surgical group, 66%; nonsurgical group, 19%

TNM: tumour, node, metastasis; ppo: predicted post-operative; DL_{CO}: diffusing capacity of the lung for carbon monoxide; LVRS: lung volume reduction surgery; VATS: video-assisted thoracic surgery; % pred: % predicted.

The majority of studies of lobectomy in patients with COPD and lung cancer [49, 51, 52, 57] conclude that post-operative PFTs in these patients are less diminished than the data from patients without COPD would suggest. A possible reason for this could be the improvement in bronchial airway obstruction related to relief of pulmonary hyperinflation, and the diaphragm's improved respiratory muscle activity secondary to lung resection and its re-positioning [49, 51, 52, 57].

The largest retrospective study was performed by SEKINE *et al.* [49] in 521 patients who underwent lobectomy for lung cancer. The authors evaluated the influence of COPD on post-operative PFTs and tried to clarify the factors for the less-than-expected reduction of PFTs after lobectomy. This study showed that in patients with COPD, arterial blood gas data were unchanged and dynamic lung volumes were less diminished when compared to the data from patients without COPD (COPD group: FEV₁ 13.1% reduction from pre-operative value; non-COPD group: FEV₁ 29.2% reduction from pre-operative value). In particular, FEV₁/forced vital capacity (FVC) ratio improved more after lobectomy in patients with COPD (17.3% increase in COPD) than in those with no COPD (3.2%). This occurred in patients with heterogeneous/homogeneous emphysema confirmed by chest CT and could be interpreted as an improvement in bronchial airway obstruction related to relief of pulmonary hyperinflation and to a better respiratory muscle activity of the diaphragm secondary to lung resection. By multivariable analysis, lower/middle-lower lobectomies were shown to be independent factors for inducing the least deterioration of post-operative FEV₁ [49]. A possible explanation is that the movement and elevation of the diaphragm after lobectomy may be different after lower and upper lobectomy [49].

One small study of 11 patients with COPD undergoing lobectomy/bilobectomy, mainly for primary lung cancer [51], did not demonstrate any significant change in FEV₁ or DL_{CO} 3 months post-operatively, but did show an important decrease of 21% in maximal oxygen uptake ($\dot{V}'\text{O}_{2,\text{max}}$) (from a mean value of 17.8 to 14.1 mL·kg⁻¹·min⁻¹). This suggests that a low post-operative FEV₁ may predict a loss of post-operative exercise capacity and a tendency of FEV₁ to underestimate exercise capacity loss following surgery. However, the study was too small to draw any definitive conclusion due both to the numbers and the wide range of their severity of COPD.

KUSHIBE *et al.* [57] performed a larger study of 100 patients with and without COPD undergoing lobectomy. They showed that patients with COPD lost less of their FEV₁ than their non-COPD counterparts (COPD with FEV₁ ≥ 80% pred: 11.6% reduction from pre-operative value; COPD with FEV₁ < 80% pred: 4.7% increase from pre-operative value; non-COPD group: 14.7% reduction from pre-operative value) and that the loss of $\dot{V}'\text{O}_{2,\text{max}}$ was similar between those without and with COPD and a normal FEV₁. However, those with mildly reduced pre-operative FEV₁ showed smaller relative decreases in $\dot{V}'\text{O}_{2,\text{max}}$ post-operatively and those with the lowest pre-operative FEV₁ values actually showed an increase in $\dot{V}'\text{O}_{2,\text{max}}$ after surgery [57].

As mentioned previously, the site of the lobe resected in the presence of COPD seems to influence post-operative lung function. There is a predilection for greater respiratory impairment following upper lobectomies [57, 59]. KUSHIBE *et al.* [57] showed that left upper lobectomy was associated with the greatest loss in $\dot{V}'\text{O}_{2,\text{max}}$ ($p < 0.05$) and with a significantly greater loss in workload than right upper or right lower lobectomy ($p < 0.05$). The association of left upper lobectomy with a greater magnitude of loss in $\dot{V}'\text{O}_{2,\text{max}}$ in the operated lung than in right upper or left lower lobectomy is thought to be linked to a narrowing of the orifice of the lower or middle lobe bronchus that may occur following upper lobectomy, but this seems highly speculative [49].

In another study, KUSHIBE *et al.* [59] compared the differences between observed and predicted post-operative (ppo) values of PFTs at different times in patients with and without COPD following a lobectomy for lung cancer. The observed and ppo percentage in changes in FEV₁ at 1 and 6 months after right or left upper lobectomy were of significantly higher positive values in patients with COPD than in those without COPD ($p < 0.05$). Patients with COPD and right upper lobectomy developed greater respiratory function impairment.

BALDI *et al.* [52] performed a retrospective multicentre national trial in 137 patients with and without COPD who underwent lobectomy. Their findings were in agreement with those of SEKINE

et al. [49] and showed that PFT after lobectomy improves, or at least diminishes less, in patients with COPD as compared with patients without COPD, and that this phenomenon is more evident in patients with more severe airway obstruction and hyperinflation. BALDI *et al.* [52] speculate, as do SEKINE *et al.* [49], that this airway improvement could be due to the relief of hyperinflation and/or chest wall mechanics. Resection of dead space in the case of local pulmonary artery involvement could be another way to explain functional amelioration in some cases [52]. Indeed, most of the pre-operative functional assessment before resection focuses on airway and parenchymal quality, and not on any possible effect on the pulmonary vascular tree. Many cancers visualised by CT encroach on or appear close to the pulmonary arteries, but the effect of this (*i.e.* increased dead space ventilation secondary to the impairment of perfusion) may not be appreciated or measured. Resection of a tumour that had a serious effect on ventilation/perfusion imbalance could result in dramatically improved post-operative value. While the studies cited here do not provide a clear association between pre- and post-operative lung function, much seems to depend on the predominant type of COPD. Thus, those with more emphysematous lungs appear to lose less function after lobectomy than those without COPD and those with airway-dependent obstruction and less loss of recoil. Whether the effect is truly lobe-dependent needs to be clarified in larger prospective studies.

Sublobar resection and the use of brachytherapy

The presence of COPD has had a limiting effect on surgeon's willingness to perform lobectomies (*i.e.* the resection of choice) due to predicted loss of lung function. As a consequence of this, sublobar resection has gained ground as it spares functioning lung parenchyma while achieving tumour and lymph node clearance. It allows more patients who would otherwise not have adequate respiratory reserve for the gold standard open lobectomy to undergo curative lung resection and improve their survival prospects [48, 53, 59]. Nevertheless, there is still a lack of good randomised controlled trials comparing lobectomy with more conservative surgical options [60]. The development of video-assisted thoracoscopic surgery (VATS) has encouraged the frequency of minor resections, not only due to the smaller amount of lung tissue removed but also due to these procedures causing less post-operative pain, quicker discharge from hospital and a lower complication rate [48, 58].

In this context, PUENTE-MAESTÚ *et al.* [48] prospectively studied 126 consecutive patients evaluated for anatomic resection of lung tumours by thoracotomy. Patients were subdivided into a surgical (pneumonectomy, (bi)lobectomy, segmentectomy or VATS wedge resection) and a nonsurgical group (radiotherapy, ablation with radiofrequency, chemoradiotherapy or supportive care). When mortality data were analysed in terms of the extent of the resection, patients of the surgical group had a 60-day mortality of 6.2% for segmentectomies, 6.5% for lobectomies and 15% for pneumonectomies. However, this survival data was not significantly different between these groups ($p > 0.1$). However, the 2-year survival was 2.5 times better for the surgical group overall compared with the nonsurgical one ($p < 0.01$).

LAU *et al.* [58] reported a small yet interesting retrospective study to compare the outcomes of combining VATS lobectomy and anatomical segmentectomy (study group) against open lobectomy (control group) in 84 consecutive patients with lung and severe pulmonary dysfunction as defined as a $\text{ppoFEV}_1 < 40\%$ pred.

The median length of hospital stay was shorter in the VATS resection group (8 *versus* 12 days, $p = 0.054$). Fewer patients in this group developed either respiratory (22% *versus* 48%, $p = 0.019$) or nonrespiratory complications (14% *versus* 34%, $p = 0.037$) and there was no significant difference in in-hospital mortality (8% *versus* 14%, $p = 0.48$). After a mean follow-up time of 56 months, recurrence was observed in 13 (27%) patients in the VATS group and seven (20%) patients in the control group ($p = 0.6$). While the incidence of distant recurrence was similar in both groups, locoregional recurrence occurred more frequently in the VATS group (14% *versus* 6%, $p = 0.29$). However, unadjusted survival was significantly longer in this group (median survival 54 *versus*

20 months, 5-year survival 42% *versus* 18%; $p=0.03$) and this survival benefit remained significant in multivariate analyses (adjusted survival HR 2.39, 95% CI 1.30–4.39; $p=0.005$). After segregating by surgical approach and the extent of resection, VATS was identified as the critical factor conferring a 2.8-fold adjusted survival benefit over the open approach (HR 2.782, 95% CI 1.215–6.371; $p=0.016$), while segmentectomy did not offer a significant benefit in survival [58].

IWASAKI *et al.* [53] retrospectively studied 50 patients with moderate or severe COPD who underwent a curative approach for lung cancer (31 lobectomies, 11 segmentectomies and eight bilobectomies). Post-operative decrease in FEV₁ was less compared with the predicted data for patients who underwent surgery for NSCLC with COPD, as already discussed. The overall 5-year survival rate for lung cancer with COPD was 73.9%, although there was no statistically significant difference between moderate and severe COPD. Patients undergoing lobectomy and segmentectomy had a better survival outcome than those undergoing a bilobectomy, although this difference was not statistically significant.

Due to the need to try to limit the extent of pulmonary resection in the presence of coexisting COPD, there still are concerns that safer, more limited resections would offer smaller chances of cure than conventional lobectomy.

GINSBERG *et al.* [61] conducted a randomised controlled trial in 247 patients with peripheral T1N0 NSCLC (≤ 3 cm) and compared limited resection with lobectomy. This study showed that patients with sublobar resections presented an observed 75% increase in recurrence rates ($p=0.02$, one sided) that was attributed to an observed three-fold increase of the local recurrence rate with wedge resection and 2.4-fold increase with segmental resection, as compared with lobectomy. This increased locoregional recurrence rate after limited resection could be attributed to inadequate resection of the primary tumour, or failure to identify and resect intrapulmonary microscopic and lymphatic tumour spread. Moreover, the patients with segmental resection had a 30% increase in overall death rate ($p=0.08$, one-sided) and an observed 50% increase in death from lung cancer ($p=0.09$, one-sided) compared with those undergoing a lobectomy.

SIENEL *et al.* [62] studied segmentectomy *versus* wedge resection in 87 patients with stage IA NSCLC (mean $\pm$ SD tumour size $\sim 1.9 \pm 0.7$ cm) (segmentectomy, 56 out of 87 patients; wedge resection, 31 out of 87 patients). They showed that wedge resection was associated with a significantly increased local recurrence rate compared with segmentectomy (55% *versus* 16%; $p=0.001$) and impaired respiratory and/or cardiac function. Follow-up CT showed that 91% of local recurrences developed in the remaining lung parenchyma where initial resections were performed, *i.e.* local recurrence. In this study, segmentectomy had a better cancer-related 5-year survival than wedge resection (71% *versus* 48%, respectively; $p=0.016$). Nevertheless, occurrence of distant metastasis was equal between the two procedures.

However, a large study of 2,090 patients with stage I NSCLC (≤ 1 cm) from the Surveillance Epidemiology and End Results (SEER) registry [63] showed that there was no difference in outcomes among patients treated with lobectomy *versus* limited resection (segmentectomy/wedge resection) (adjusted HR for overall survival 1.12, 95% CI 0.93–1.35; lung cancer-specific survival HR 1.24, 95% CI 0.95–1.61). However, that group of patients was diagnosed with smaller tumours (<1 cm) as compared to patients in the other studies [61, 62].

PETTIFORD *et al.* [64] suggest that sublobar resection could be an appropriate therapy for the management of stage I NSCLC identified in the elderly and those individuals with significant cardiopulmonary dysfunction, and for peripheral solitary metastatic disease of the lung. As mentioned earlier [61–63], due to the fact that the primary disadvantage of sublobar resection is that of local recurrence, intraoperative adjuvant iodine-125 brachytherapy may be considered to minimise this local recurrence risk [60, 64–66].

A study by SANTOS *et al.* [65] compared patients with poor cardiopulmonary reserve and stage I NSCLC who underwent segmental resection alone (102 out of 203 patients) with patients (101 out of 203 patients) who underwent segmental resection and intraoperative iodine-125 brachytherapy

placed over the segmental resection staple line. Local recurrence after segmental resection and iodine-125 brachytherapy (2%) (median follow-up 18 months) was significantly less than after segmental resection alone (18.6%) (median follow-up 24–29 months). This is a promising result as iodine-125 brachytherapy is immediate and devoid of associated loss in PFT on subsequent follow-up at 6-month intervals after surgery [65].

A retrospective multicentre study of 291 patients with T1N0 disease (diameter <3 cm) compared outcomes after sublobar resection (n=124) with those after lobar resection (n=167) [66]. Brachytherapy was used in conjunction with 60 (48%) sublobar resection operations and reduced the local recurrence that was usually reported with sublobar resection. In the 124 patients undergoing sublobar resection, local recurrence was seen after seven (9.6%) of the segmentectomies and six (11.8%) of the wedge resections. These rates were not significantly different ($p=0.725$). However, the use of brachytherapy significantly ($p=0.012$) decreased the incidence of local recurrence, from 11 (17.2%) to two (3.3%) patients.

Intraoperative brachytherapy on the grounds of segmental resection in patients not eligible for lobectomy seems an attractive approach, although larger series of studies are necessary to confirm that and introduce it into standard clinical practice.

Pneumonectomy

There are only a few small studies addressing pneumonectomy and patient outcomes in terms of PFTs and survival in patients with COPD undergoing surgical resection for lung cancer [48, 54, 67].

As stated in the previous section, PUENTE-MAESTÚ *et al.* [48] studied 126 consecutive patients evaluated for anatomic resection of lung tumours by thoracotomy. 2-year survival was significantly better (at least 2.5 times greater) for the surgical group (pneumonectomy, (bi)lobectomy, anatomic segmentectomy or VATS wedge resection) compared with the nonsurgical one (radiotherapy, ablation with radiofrequency, chemoradiotherapy or supportive care) ($p<0.01$). However, pneumonectomies were not studied *per se* in terms of patient outcome and were integrated with the rest of surgical procedures performed for resection.

SUBOTIC *et al.* [54] studied 82 patients (35 with COPD and 47 with normal lung function) who underwent lobectomy and pneumonectomy for lung cancer. Post-operative changes in FEV₁ in both the COPD and control groups (normal PFT) confirmed the relatively mild permanent lung function loss after lobectomy, unlike the early permanent loss in lung function of approximately 33% that occurs after pneumonectomy. In the COPD group, the reduction in FEV₁ was significantly lower than that in the control group, both in patients with lobectomy (12% *versus* 25%) and pneumonectomy (18% *versus* 43%). One of the most significant results of this study [54] is an important improvement of small airway function (mean improvement in: forced expiratory flow at 50% of FVC (FEF_{50%}) 18.14%; FEF_{25%} 25.59%) registered after lobectomy in patients with limited lung function. In patients who underwent a pneumonectomy, the 23.31% mean improvement of FEF_{50%} in those with COPD was not statistically significant. These results are of practical interest because of the direct influence on the pattern of post-operative lung function change. Operative mortality and morbidity in patients with COPD were comparable to those in patients with normal lung function.

Combined lung volume reduction surgery and lung cancer resection

Lung cancer is associated with the development of emphysema. Studies looking to improve lung function in those having localised, often upper lobe emphysema and undergoing lung volume reduction surgery (LVRS), also found “hidden” stage I cancers at resection. The fact that most well-chosen subjects undergoing LVRS had an improvement, at least in the short term, in overall lung function led to LVRS becoming a good treatment for lobar emphysema and an associated lung tumour. Resection of a hyperinflated and poorly perfused lobe that contains a malignant tumour balances any functional loss and complication risks. MCKENNA *et al.* [68] reported a series

of 325 patients who underwent LVRS, 51 of whom presented with a pulmonary mass in addition to the emphysema (11 out of 51 patients had NSCLC). These 51 patients underwent combined LVRS and resection of lung cancer (lobectomy/wedge resection). There was no perioperative mortality and no recurrence of lung cancer after a 9-month follow-up. Average pre-operative FEV₁ was 0.65 L compared with 1.08 L post-operatively and seven out of 11 patients improved their dyspnoea score. The patients having lung cancer in a lobe already targeted for LVRS were the ones presenting the most benefit in PFTs. This could generate the idea that patients with severe COPD who were rejected in the past for curative surgery on the grounds of lung cancer may have gained functional benefit in terms of PFTs and severity of dyspnoea.

Based on that, EDWARDS *et al.* [69] tried to apply LVRS to remove a lobe containing lung cancer. They studied 29 patients with a resectable lung cancer within a poorly perfused, hyperinflated emphysematous lobe. Patients were stratified according to their ppoFEV₁. There was a higher perioperative mortality in patients with ppoFEV₁ <40% pred and there were no deaths in the group of patients with ppoFEV₁ >40% pred. Nevertheless, a median follow up of 12 months in both groups of patients did not reveal any difference in mortality between them. In addition to that, the authors did not find any difference between the pre- and post-operative value of FEV₁ in patients with ppoFEV₁ <40% pred. This study concluded that the use of standard calculations of ppoFEV₁ to select emphysematous patients for lung cancer resection can be misleading, and that the effect of lobar LVRS should also be taken into account and could probably allow the extension of the selection criteria for surgery.

Application of both LVRS and lung cancer resection in highly selected patients diagnosed with both COPD and lung cancer is more likely to be successful if the tumour is located in a part of the lung already targeted for LVRS. Each subject should be considered carefully and thoroughly in the aspect of maximising the number of patients undergoing successful curative resections for lung cancer.

Radiation therapy

Patients with severe respiratory function impairment that does not meet the criteria for surgery (table 1) may benefit from radiation therapy, which can provide results in stage I disease that are comparable with surgery.

However, there are no clear cut-off values of PFTs that could prohibit surgery, particularly in the presence of localised emphysema, making them more suitable for radiation therapy. It would be even more interesting to have a stratification of eligibility criteria for each radiotherapeutic modality, *i.e.* PFT cut-off values for three-dimensional conformal radiation therapy, for intensity-modulated radiation therapy (IMRT), *etc.* Further studies in this direction are necessary that would offer a refinement of the current guidelines and would clearly include eligibility criteria for each type of radiation therapy that could be applied to surgically nonresectable lung cancers in patients with severe COPD. Currently, there is limited data associating pre-morbid physiology with radiation toxicity [45] and radiotherapists remain relatively oblivious to the benefits of careful lung function testing. However, several chemoradiotherapy trials have used pulmonary function values similar to those used to assess potential patients [45].

PALMA *et al.* [70] recently showed that in stage I disease, stereotactic body radiotherapy (SBRT) offers local or locoregional control as high ($\geq 89\%$) as surgery while overall survival is comparable between the two therapeutic options (post-SBRT, 79–95% at 1 year and 43–70% at 3 years *versus* post-surgical, 45–86% at 1 year and 31–66% at 3 years). The mean 30-day mortality rate post-SBRT was 0% compared with 10% post-surgery.

Innovative radiotherapy planning and applications seem to present promising results. KIMURA *et al.* [71] recently showed that functional image-guided radiotherapy planning based on low-attenuation areas in respiratory-guided IMRT or volumetric modulated arc therapy (VMAT) appears to be effective in preserving a functional lung in lung cancer patients with severe COPD.

Although the data seem promising, they are scarce in the literature and do not offer robust conclusions that could be considered for application in everyday clinical practice. More research with larger groups of patients and follow-up is needed to further clarify and validate this.

Common underlying mechanisms between COPD and lung cancer

The most possible common underlying mechanism between COPD and lung cancer is a chronic smouldering inflammation secondary to cigarette smoke exposure, which supports the old Virchow theory that cancer occurs in sites where chronic inflammation is well established [72]. DVORAK [73] defined tumours as “wounds that do not heal” and showed that tumour stroma and wound repair share important properties.

Cigarette smoke triggers the recruitment and activation of macrophages and neutrophils that release matrix metalloproteinases and reactive oxygen species, which cause the physiological changes observed in COPD and/or lung cancer [74–77]. Immune inflammatory pathways and epigenetics are thought to contribute to the increased risk of COPD patients for developing lung cancer [75]. Epithelial–mesenchymal transition, abnormal repair, oxidative stress and cell proliferation seem to play their role in the common underlying mechanisms binding the two diseases and lead to extensive remodelling [76].

Smokers with a genetic susceptibility to an exaggerated response to cigarette smoking could be at increased risk of lung cancer as the extensive airway remodelling leads to epithelial–mesenchymal transition that, in turn, is thought to promote malignant transformation in the respiratory epithelium [78]. However, the exact reason why some smokers develop COPD, some develop cancer and some develop both diseases is not known [79]. Recent studies [80–83] have proposed chromosomal loci and/or candidate genes associated with lung function, COPD and lung cancer, including 1q21–23 (*CRP* and *IL6R*), 4q22 (*FAM13A*), 4q24 (*GSTCD*) and 4q31 (*HHIP* and *GYP A*). Further studies are needed to examine the shared genetic network between these diseases.

Conclusion

COPD and lung cancer are strongly associated and coexist in a large number of patients. Smoking remains responsible for the majority of cases of COPD and lung cancer, and is still a major public health issue despite public health initiatives. Treating lung cancer patients with severe COPD presents a clinical challenge for thoracic physicians and warrants a multidisciplinary approach. Identifying smokers at the greatest risk of COPD and/or lung cancer seems to be a necessity in terms of public health and would herald a new era in preventive medicine. It would be very useful to further understand the overlapping pathways of COPD and lung cancer, derive risk models for lung cancer that will include lung cancer-specific genetic variants, recently identified “COPD-related” genetic variants and clinical variables, and stratify patients accordingly. In this way, targeting smokers for low-dose CT screening for early detection of lung cancer would be a possible application presenting exciting future possibilities.

Statement of Interest

None declared.

References

1. Rosen G. A History of Public Health. Baltimore, The Johns Hopkins University Press, 1993.
2. Boyle P, Smans M. Atlas of Cancer Mortality in the European Union and the European Economic Area 1993–1997. IARC Scientific Publication No. 159. Lyon, International Agency for Research on Cancer, 2008.
3. Parkin DM, Bray F, Ferlay J, *et al.* Global Cancer Statistics, 2002. *CA Cancer J Clin* 2005; 55: 74–108.
4. GLOBOCAN 2008. Lung Cancer Incidence and Mortality Worldwide in 2008. <http://globocan.iarc.fr/factsheets/cancers/lung.asp> Date last accessed: May 3, 2012. Date last updated: December 17, 2012.

5. World Health Organisation. Cancer. Fact sheet No. 297. www.who.int/mediacentre/factsheets/fs297/en/ Date last accessed: May 3, 2012. Date last updated: February 2012.
6. Howlader N, Noone AM, Krapcho M, *et al*. SEER Cancer Statistics Review, 1975–2008. http://seer.cancer.gov/csr/1975_2008/ Date last accessed: August 26, 2012. Date last updated: 2011.
7. Global Initiative for Chronic Obstructive Pulmonary Disease. Revised 2011. p. vii. Available from www.goldcopd.org Date last accessed: August 26, 2012..
8. World Health Organization. Chronic Respiratory Diseases: Burden of COPD. www.who.int/respiratory/copd/burden/en.
9. Lopez AD, Shibuya K, Rao C, *et al*. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* 2006; 27: 397–412.
10. Menezes AM, Perez-Padilla R, Jardim JR, *et al*. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005; 366: 1875–1881.
11. Halbert RJ, Natoli JL, Gano A, *et al*. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28: 523–532.
12. Fukuchi Y, Nishimura M, Ichinose M, *et al*. COPD in Japan: the Nippon COPD Epidemiology study. *Respirology* 2004; 9: 458–465.
13. Hasan SU. ATS statement – cigarette smoking and health. *Am J Respir Crit Care Med* 1996; 154: 1579–1580.
14. Van den Eeden SK, Friedman GD. Forced expiratory volume (1 second) and lung cancer incidence and mortality. *Epidemiology* 1992; 3: 253–257.
15. Kuller LH, Ockene J, Meilahn E, *et al*. Relation of forced expiratory volume in one second (FEV1) to lung cancer mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Epidemiol* 1990; 132: 265–274.
16. Hole DJ, Watt GC, Davey-Smith G, *et al*. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313: 711–716.
17. De Torres JP, Marín JM, Casanova C, *et al*. Lung cancer in patients with chronic obstructive pulmonary disease – incidence and predicting factors. *Am J Respir Crit Care Med* 2011; 184: 913–919.
18. De Torres JP, Bastarrika G, Wisnivesky JP, *et al*. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest* 2007; 132: 1932–1938.
19. Kiri VA, Soriano J, Visick G, *et al*. Recent trends in lung cancer and its association with COPD: an analysis using the UK GP Research Database. *Prim Care Respir J* 2010; 19: 57–61.
20. Mannino DM, Aguayo SM, Petty TL, *et al*. Low lung function and incident lung cancer in the United States: data from the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003; 163: 1475–1480.
21. Wilson DO, Weissfeld JL, Balkan A, *et al*. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med* 2008; 178: 738–744.
22. Wasswa-Kintu S, Gan WQ, Man SF, *et al*. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax* 2005; 60: 570–575.
23. Gullón JA, Suárez I, Medina A, *et al*. Role of emphysema and airway obstruction in prognosis of lung cancer. *Lung Cancer* 2011; 71: 182–185.
24. Cassidy A, Myles JP, Liloglou T, *et al*. Defining high-risk individuals in a population-based molecular-epidemiological study of lung cancer. *Int J Oncol* 2006; 28: 1295–1301.
25. Turner MC, Chen Y, Krewski D, *et al*. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med* 2007; 176: 285–290.
26. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. *Ann Intern Med* 1986; 105: 503–507.
27. Brody JS, Spira A. State of the art. Chronic obstructive pulmonary disease, inflammation, and lung cancer. *Proc Am Thorac Soc* 2006; 3: 535–537.
28. Gold DR, Wang X, Wypij D, *et al*. Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med* 1996; 335: 931–937.
29. Xu X, Weiss ST, Rijcken B, *et al*. Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. *Eur Respir J* 1994; 7: 1056–1061.
30. Prescott E, Bjerg AM, Andersen PK, *et al*. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997; 10: 822–827.
31. Connett JE, Murray RP, Buist AS, *et al*. Changes in smoking status affect women more than men: results of the Lung Health Study. *Am J Epidemiol* 2003; 157: 973–979.
32. Risch HA, Howe GR, Jain M, *et al*. Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. *Am J Epidemiol* 1993; 138: 281–293.
33. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst* 1996; 88: 183–192.
34. Osann KE, Anton-Culver H, Kurosaki T, *et al*. Sex differences in lung-cancer risk associated with cigarette smoking. *Int J Cancer* 1993; 54: 44–48.
35. Bain C, Feskanich D, Speizer FE, *et al*. Lung cancer rates in men and women with comparable histories of smoking. *J Natl Cancer Inst* 2004; 96: 826–834.

36. Henschke CI, Yip R, Miettinen OS. Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer. *JAMA* 2006; 296: 180–184.
37. Loganathan RS, Stover DE, Shi W, *et al.* Prevalence of COPD in women compared to men around the time of diagnosis of primary lung cancer. *Chest* 2006; 129: 1305–1312.
38. Ben-Zaken Cohen S, Paré PD, Man SF, *et al.* The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. *Am J Respir Crit Care Med* 2007; 176: 113–120.
39. Young RP, Hopkins RJ, Christmas T, *et al.* COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. *Eur Respir J* 2009; 34: 380–386.
40. Buist AS, McBurnie MA, Vollmer WM, *et al.* International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370: 741–750.
41. Mina N, Soubani AO, Cote ML, *et al.* The relationship between chronic obstructive pulmonary disease and lung cancer in African American patients. *Clin Lung Cancer* 2012; 13: 149–156.
42. McCaughan F, Spiro SG. Management of patients with COPD. *Lancet* 2004; 364: 2015.
43. British Thoracic Society, Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party. Guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001; 56: 89–108.
44. Brunelli A, Charloux A, Bolliger CT, *et al.* The European Respiratory Society and European Society of Thoracic Surgeons clinical guidelines for evaluating fitness for radical treatment (surgery and chemoradiotherapy) in patients with lung cancer. *Eur J Cardiothorac Surg* 2009; 36: 181–184.
45. Colice GL, Shafazand S, Griffin JP, *et al.* Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007; 132: Suppl. 3, 161S–177S.
46. Bolliger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. *Eur Respir J* 1998; 11: 198–212.
47. Licker MJ, Widikker I, Robert J, *et al.* Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg* 2006; 81: 1830–1837.
48. Puente-Maestú L, Villar F, González-Casurrán G, *et al.* Early and long-term validation of an algorithm assessing fitness for surgery in patients with postoperative FEV1 and diffusing capacity of the lung for carbon monoxide < 40%. *Chest* 2011; 139: 1430–1438.
49. Sekine Y, Iwata T, Chiyo M, *et al.* Minimal alteration of pulmonary function after lobectomy in lung cancer patients with chronic obstructive pulmonary disease. *Ann Thorac Surg* 2003; 76: 356–361.
50. Choong CK, Meyers BF, Battafarano RJ, *et al.* Lung cancer resection combined with lung volume reduction in patients with severe emphysema. *J Thorac Cardiovasc Surg* 2004; 127: 1323–1331.
51. Bobbio A, Chetta A, Carbognani P, *et al.* Changes in pulmonary function test and cardio-pulmonary exercise capacity in COPD patients after lobar pulmonary resection. *Eur J Cardiothorac Surg* 2005; 28: 754–758.
52. Baldi S, Ruffini E, Harari S, *et al.* Does lobectomy for lung cancer in patients with chronic obstructive pulmonary disease affect lung function? A multicenter national study. *Thorac Cardiovasc Surg* 2005; 130: 1616–1622.
53. Iwasaki A, Shirakusa T, Enatsu S, *et al.* Surgical treatment for lung cancer with COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Thorac Cardiovasc Surg* 2005; 53: 162–167.
54. Subotic DR, Mandaric DV, Eminovic TM, *et al.* Influence of chronic obstructive pulmonary disease on postoperative lung function and complications in patients undergoing operations for primary non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2007; 134: 1292–1299.
55. Schattenberg T, Muley T, Dienemann H, *et al.* Impact on pulmonary function after lobectomy in patients with chronic obstructive pulmonary disease. *Thorac Cardiovasc Surg* 2007; 55: 500–504.
56. Martin-Ucar AE, Fareed KR, Nakas A, *et al.* Is the initial feasibility of lobectomy for stage I non-small cell lung cancer in severe heterogeneous emphysema justified by long-term survival? *Thorax* 2007; 62: 577–580.
57. Kushibe K, Kawaguchi T, Kimura M, *et al.* Exercise capacity after lobectomy in patients with chronic obstructive pulmonary disease. *Interact Cardiovasc Thorac Surg* 2008; 7: 398–401.
58. Lau K, Martin-Ucar AE, Nakas A, *et al.* Lung cancer surgery in the breathless patient — the benefits of avoiding the gold standard. *Eur J Cardiothorac Surg* 2010; 38: 6–13.
59. Kushibe K, Kawaguchi T, Michitaka Kimura M, *et al.* Influence of the site of lobectomy and chronic obstructive pulmonary disease on pulmonary function: a follow-up analysis. *Interact CardioVasc Thorac Surg* 2009; 8: 529–533.
60. Narsule CK, Ebright MI, Fernando HC, *et al.* Sublobar versus lobar resection: current status. *Cancer J* 2011; 17: 23–27.
61. Ginsberg RJ, Rubinstein LV, Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. *Ann Thorac Surg* 1995; 60: 615–622.
62. Sielens W, Dango S, Kirschbaum A, *et al.* Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. *Eur J Cardiothorac Surg* 2008; 33: 728–734.
63. Kates M, Swanson S, Wisnivesky JP, *et al.* Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer ≤ 1 cm in size: a review of SEER data. *Chest* 2011; 139: 491–496.
64. Pettiford BL, Schuchert MJ, Santos R, *et al.* Role of sublobar resection (segmentectomy and wedge resection) in the surgical management of non-small cell lung cancer. *Thorac Surg Clin* 2007; 17: 175–190.
65. Santos R, Colonias A, Parda D, *et al.* Comparison between sublobar resection and ¹²⁵Iodine brachytherapy after sublobar resection in high-risk patients with stage I non-small cell lung cancer. *Surgery* 2003; 134: 691–697.

66. Fernando HC, Santos RS, Benfield JR, *et al.* Lobar and sublobar resection with and without brachytherapy for small stage IA non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2005; 129: 261–267.
67. Volpino P, Cangemi R, Fiori E, *et al.* Risk of mortality from cardiovascular and respiratory causes in patients with chronic obstructive pulmonary disease submitted to follow-up after lung resection for non-small cell lung cancer. *J Cardiovasc Surg (Torino)* 2007; 48: 375–383.
68. McKenna RJ Jr, Fischel RJ, Brenner M, *et al.* Combined operations for lung volume reduction surgery and lung cancer. *Chest* 1996; 110: 885–888.
69. Edwards JG, Duthie DJ, Waller DA. Lobar volume reduction surgery: a method of increasing the lung cancer resection rate in patients with emphysema. *Thorax* 2001; 56: 791–795.
70. Palma D, Lagerwaard F, Rodrigues G, *et al.* Curative treatment of Stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. *Int J Radiat Oncol Biol Phys* 2012; 82: 1149–1156.
71. Kimura T, Nishibuchi I, Murakami Y, *et al.* Functional image-guided radiotherapy planning in respiratory-gated intensity-modulated radiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Int J Radiat Oncol Biol Phys* 2012; 82: e663–e670.
72. David H. Rudolf Virchow and modern aspects of tumor pathology. *Pathol Res Pract* 1988; 183: 356–364.
73. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 1986; 315: 1650–1659.
74. Spira A, Beane J, Shah V, *et al.* Effects of cigarette smoke on the human airway epithelial cell transcriptome. *Proc Natl Acad Sci USA* 2004; 101: 10143–10148.
75. Adcock IM, Caramori G, Barnes PJ. Chronic obstructive pulmonary disease and lung cancer: new molecular insights. *Respiration* 2011; 81: 265–284.
76. Yang IA, Relan V, Wright CM, *et al.* Common pathogenic mechanisms and pathways in the development of COPD and lung cancer. *Expert Opin Ther Targets* 2011; 15: 439–456.
77. Houghton AM, Mouded M, Shapiro S. Clearing the smoke. *Nat Med* 2008; 14: 1023–1034.
78. Young RP, Hopkins RJ. How the genetics of lung cancer may overlap with COPD. *Respirology* 2011; 16: 1047–1055.
79. Brody JS, Spira A. State of the art. Chronic obstructive pulmonary disease, inflammation, and lung cancer. *Proc Am Thorac Soc* 2006; 3: 535–537.
80. Thorgeirsson TE, Geller F, Sulem PA, *et al.* variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature*. 2008; 452: 638–642.
81. Young RP, Hopkins RJ, Hay BA, *et al.* Lung cancer gene associated with COPD: triple whammy or possible confounding effect? *Eur Respir J* 2008; 32: 1158–1164.
82. Pillai SG, Ge D, Zhu G, *et al.* A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. *PLoS Genet* 2009; 5: e1000421.
83. Young RP, Hopkins RJ, Gamble GD, *et al.* Genetic evidence linking lung cancer and COPD: a new perspective. *Appl Clin Genet* 2011; 4: 1–13.

Chapter 14

Pulmonary hypertension in COPD



Jordanna Hostler*, A. Whitney Brown[#], John Sherner[¶],
Christopher S. King[¶] and Steven D. Nathan[#]

SUMMARY: Pulmonary hypertension (PH) commonly complicates COPD, with an estimated prevalence of 20–63%. Most PH in COPD is mild-to-moderate in severity, although a small proportion of patients develop PH “out of proportion” to their degree of airflow obstruction. The development of PH is associated with worsened functional status and decreased survival. The pathogenesis of COPD-associated PH is incompletely understood but is believed to result from a complex interplay of inflammation, endothelial dysfunction and vascular remodelling due to hypoxia and cigarette smoke, mechanical factors resulting from air-trapping, and host genetic factors. Physical examination, ECG and radiographic findings may be suggestive of PH but are nonspecific. Echocardiography is useful as a screening tool for PH but may over- or underestimate pulmonary pressures. Right heart catheterisation remains the gold standard for diagnosis. Treatment is focused on smoking cessation, optimal therapy of COPD and supplemental oxygen. There is interest in vasodilator therapy for COPD-associated PH, particularly for those with out-of-proportion PH; however, this approach requires further evaluation in clinical trials.

KEYWORDS: COPD, endothelin receptor antagonist, phosphodiesterase-5 inhibitors, pulmonary hypertension, right heart catheterisation

*Dept of Medicine, Division of Pulmonary and Critical Care Medicine, Walter Reed National Military Medical Center, Bethesda, MD,

[#]Advanced Lung Disease and Transplant Program, Dept of Medicine, Inova Fairfax Hospital, Falls Church, VA, and

[¶]Dept of Medicine, Division of Pulmonary and Critical Care Medicine, Fort Belvoir Community Hospital, Alexandria, VA, USA.

Correspondence: S.D. Nathan, Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, 3300 Gallows Road, Falls Church, VA, 22042, USA.
Email: steven.nathan@inova.org

Eur Respir Monogr 2013; 59: 189–205.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10012412
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

One of the common complications of COPD is pulmonary hypertension (PH), and the two are pathologically interdependent. COPD-associated PH is increasingly recognised as a marker of poor prognosis. It is associated with an increased risk of exacerbations and with worsened exercise capacity, oxygenation and mortality [1–5]. The true incidence, prevalence and ideal management strategies for COPD-associated PH are unknown. Right heart catheterisation (RHC) is compulsory to establish a definitive diagnosis. The mainstays of therapy continue to be: optimisation of overall COPD management with oxygen, smoking cessation and bronchodilators; pulmonary rehabilitation; and lung transplantation or lung volume reduction surgery (LVRs) for appropriate candidates [6, 7]. However, the advent of advanced therapy for pulmonary arterial

hypertension (PAH) has sparked interest in pharmacological treatments for PH beyond World Health Organization (WHO) group I.

This chapter reviews past and recent developments in the definition, epidemiology, genetics, pathophysiology, diagnosis, treatment and prognosis of COPD-associated PH.

Definition

The definition of COPD-associated PH has evolved over time. In earlier investigations, a mean pulmonary artery pressure (mPAP) of >20 mmHg was considered diagnostic for PH in respiratory disease [2, 3, 8, 9]. PH was initially defined as mPAP ≥ 25 mmHg at rest and ≥ 30 mmHg during exercise. The 4th World Symposium on Pulmonary Hypertension simplified matters by defining PH as mPAP ≥ 25 mmHg measured by RHC. The diagnosis of PH during exercise was eliminated [10]. PH is further subdivided into five groups based on aetiology, with COPD-associated PH included in WHO group 3 [11].

Echocardiography has been used to screen for PH, which is suggested by a tricuspid insufficiency peak gradient of ≥ 30 mmHg, a tricuspid jet velocity of $2.8\text{--}3.4\text{ m}\cdot\text{s}^{-1}$ or an estimated systolic pulmonary artery pressure (sPAP) of $>36\text{--}51$ mmHg [10, 12]. However, comparative studies have found echocardiography to be inaccurate in determining PAP when compared with RHC [13, 14].

Epidemiology

The overall reported prevalence of PH in COPD ranges 20–63% [5, 15, 16]. It is difficult to define this prevalence exactly, as the diagnostic criteria used in the literature vary with differing RHC pressures and echocardiographic thresholds. Patient populations also differ and run the spectrum from primary care-based community cohorts to patients being evaluated for either LVRS or lung transplantation. The latter are inherently patients with more severe decrements in forced expiratory volume in 1 second (FEV₁) and functional class, and hence, a higher prevalence of PH [8, 17, 18]. PH is associated with worse pre-bronchodilator FEV₁ and more severe hypoxaemia. With regard to the latter, it is unclear whether the hypoxaemia is driving the PH or *vice versa*. Indeed, it is conceivable that, if left uncorrected, hypoxaemia may result in a positive feedback loop with ongoing perpetuation of the underlying PH. There does appear to be an influence of age and sex on the predisposition for PH in COPD. PH is more commonly described in patients with advanced age, but whether this association is attributable to age alone, or other comorbidities

contributing to PH in the elderly, is unclear [16, 19]. One study found PH to be more common in females exposed to smoke from biomass fuels [20].

PH associated with COPD tends to be mostly mild to moderate in severity (fig. 1). However, PH “out of proportion” to the severity of airflow obstruction is increasingly noted and may represent a distinct clinical entity that could potentially be amenable to vasoactive therapy. In a study of 215 patients referred for LVRS or transplant, 7.4% of patients had a modest decrement in FEV₁ (48% predicted) in association with a markedly elevated mPAP (39.8 mmHg) [17]. Our own data (unpublished) of 190 RHCs in a cohort of advanced COPD patients suggests a very similar proportion of such patients (fig. 1).

Given the prevalence of PH in COPD and its effect on outcomes there is value in screening for its presence. RHC cannot be used as a screening tool given its

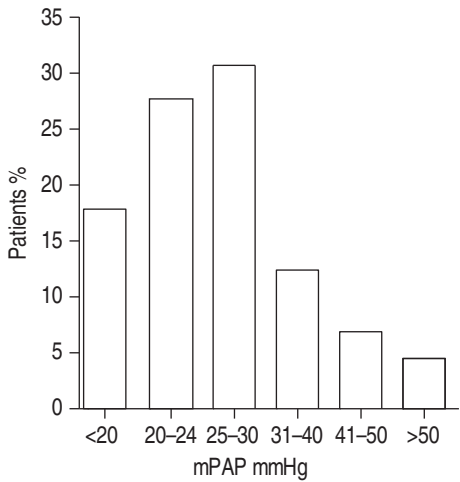


Figure 1. Mean pulmonary artery pressure (mPAP) in a cohort of 190 COPD patients.

invasive nature and expense, so echocardiography has been used to identify COPD patients with PH. One recent prospective study screened primary care-based COPD patients with echocardiography. Patients were excluded if they had congestive heart failure (CHF), a left ventricular ejection fraction less than 50% and other factors that could contribute to elevated PAP. A score derived from age, pre-bronchodilator FEV₁, desaturation and 6-minute walk performance was calculated to predict the presence of an elevated sPAP. The prevalence of PH in this community-based cohort was 63% [16]. Table 1 summarises the studies that have examined the prevalence of PH in COPD [1–5, 8, 9, 15–22].

Prognostic implications

The presence of PH is suggestive of a poor prognosis in COPD patients, as several studies correlate elevated PAP with worsened survival [1, 2, 5, 21, 23–25]. In a longitudinal study of COPD patients who underwent RHC, BURROWS *et al.* [5] found that pulmonary vascular resistance (PVR) was inversely proportional to survival; indeed, this parameter was slightly more predictive of respiratory death than FEV₁. In a recent cohort of patients referred for lung transplant evaluation, those with PH had a decreased 5-year survival compared with those with normal PAP (37% *versus* 63%) [1]. Another report determined that over a 7-year follow-up using the actuarial method, patients with mPAP ≥ 20 mmHg had a survival of 29.2% as opposed to 55.6% in the group with normal PAP [2]. In a 5-year observational series, COPD patients with PH who were receiving long-term oxygen therapy had a mortality rate of 62%, whereas those without PH had a mortality rate of 36% [23]. A trial that analysed mPAP in patients with mild-to-moderate hypoxaemia found it to have more prognostic value than arterial oxygen tension (P_{a,O_2}) [24]. In addition, being aged >60 years and a mPAP >30 mmHg were found to be the only variables associated with increased mortality in a retrospective review of patients with severe COPD who used long-term oxygen therapy. Other variables, including FEV₁, inspiratory vital capacity and P_{a,O_2} , did not correlate with mortality [25]. It is interesting to speculate that the reason the BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index performs better in predicting outcomes in COPD is because it captures elements that are impacted by the presence of underlying PH, including both the Medical Research Council (MRC) score and the 6-minute walk test distance [26].

In addition to its association with mortality, the presence of PH also has a significant morbidity implication. PH is associated with exercise-induced desaturation and reduced exercise performance during the 6-minute walk test [21, 27]. Even mild elevations in the mPAP (>18 mmHg) have been associated with an increased risk of COPD exacerbations and hospitalisation [4]. It has also recently been demonstrated that the size of the pulmonary artery segment in relation to the size of the ascending aorta, as assessed using standard computed tomography (CT), is predictive of subsequent acute exacerbations [28]. The inference from this latter study is that the pulmonary artery segment size might be predictive of underlying PH. A cursory evaluation of our own COPD patient population with RHC data (unpublished) suggests that this association might exist (fig. 2); however, this requires further validation studies.

Numerous studies have demonstrated that both the estimated sPAP on echocardiography and the mPAP on RHC have an association with subsequent survival; this raises the issue as to whether it is the average representation of the pulmonary vascular pressure (mPAP) or the maximal pressure generated (sPAP) that best predicts outcomes. If it is the latter, then this in turn raises the issue as to whether it is the PH itself that is driving outcomes or whether the PH is a physiological surrogate for other parenchymal aberrations.

Pathophysiology

The mechanisms underlying the development of PH in COPD remain incompletely understood, although there have been significant advances in understanding in recent years. It is likely that

Table 1. Studies reporting the prevalence of pulmonary hypertension (PH) in COPD

First author [ref.]	Subjects n	Design	PH diagnosis	COPD severity	Prevalence	Comments
M'YKLAND HILDE [15]	98	Prospective	RHC mPAP >25 mmHg	GOLD II-IV	26%	Elevated resting PAP predicted poor 6-minute walk distance PH by stage: II, 5%; III, 27%; IV, 53% Rates of PH were higher in females and those with biomass fuel exposure
SERTOULLARINDAN [20]	600	Retrospective	Echocardiography sPAP >35 mmHg	GOLD II-IV	54%	Worse prognosis in the PH group PH did not impact on post-transplant survival
ANDERSEN [1]	409	Retrospective	RHC mPAP >25 mmHg PAOP ≤15 mmHg	Mean ± sd FEV ₁ 23 ± 7% pred	35.7%	A composite score of age, FEV ₁ , desaturation and 6-minute walk distance predicted a risk of elevated PAP
GARTMAN [16]	86	Prospective	Echocardiography sPAP >35mmHg (94 enrolled, 86 with measureable sPAP)	Mean FEV ₁ 44.8% pred with PH, 47.3% pred without PH	63%	Increasing age and lower pre-bronchodilator FEV ₁ correlated with PH 15% of the study population could be candidates for further evaluation for pharmacologic therapy
FAYNGERSH [19]	105	Retrospective	Echocardiography sPAP >36 mmHg	Mean FEV ₁ 51.8% pred with PH, 67.2% pred without PH	60%	PH was an independent risk factor for death whilst on the lung transplant waiting list
CUTTICA [21]	4930	Retrospective	RHC mPAP >25 mmHg PAOP ≤15 mmHg	Mean ± sd FEV ₁ in PH 22 ± 10.4% pred	30.4%	Subgroup with moderate decrease in FEV ₁ with severe PH and worsened oxygenation
THABUT [17]	215	Retrospective	RHC mPAP >25 mmHg	Mean FEV ₁ 24.3% pred	50.2%	Only focused on severe PH without other causes in COPD patients and suggested treating these patients in the same way as IPAH patients
CHAOUAT [18]	998	Retrospective	RHC PAP ≥ 40 mmHg	Mean FEV ₁ 50% pred	1%	Results may be confounded; 61.4% of patients also had a wedge pressure >12 mmHg (12–20 mmHg)
SCHARF [8]	120	Prospective	RHC mPAP >20 mmHg End-expiratory sPAP >30 mmHg	Mean FEV ₁ 27% pred	90.8%	PH correlated with worsening FEV ₁ , K _{CO} , D _{L,CO}
HIGHAM [22]	73	Prospective	Echocardiography TTPG >30 mmHg	Mean FEV ₁ 39.4% pred	55% Measurable TR jet in 56 out of 73	

Table 1. Continued.

First author [ref.]	Subjects n	Design	PH diagnosis	COPD severity	Prevalence	Comments
KESSLER [4]	131	Prospective	RHC (initial) mPAP <20 mmHg	Mean $\pm$ sd FEV ₁ 44.6 $\pm$ 15.7%	0%, 25%	Observed COPD patients without PH over mean $\pm$ sd 6.8 $\pm$ 2.9 years; 25% developed PH Higher initial mPAP (rest and exercise) correlated with development of PH
OSWALD-MAMMOSSER [9]	63	Retrospective	RHC mPAP >20 mmHg	mPAP: 20 had a mean $\pm$ sd FEV ₁ 1.41 $\pm$ 0.71 L; 21–30 had FEV ₁ 1.03 $\pm$ 0.37 L; >30 had FEV ₁ 0.89 $\pm$ 0.34 L	65%	Compared echocardiography, ECG, radiological measurements and myocardial scintigraphy with RHC Echocardiography was the most sensitive (78%) and specific (75%)
WEITZENBLUM [3]	93	Prospective	RHC mPAP >20 mmHg	Mean $\pm$ sd FEV ₁ of patients with PH 1.17 $\pm$ 0.39 L	34%	Haemodynamic worsening was seen in 29%; those patients also had marked worsening of hypoxaemia
WEITZENBLUM [2]	175	Prospective	RHC sPAP >20 mmHg	Mean FEV ₁ /VC 40.2%	35%	Worse 4- and 7-year mortality in the PH group
BURROWS [5]	50	Prospective	RHC >26 mmHg at rest	Mean FEV ₁ 37.1%	20%	Survival inversely related to PVR

RHC: right heart catheterisation; mPAP: mean pulmonary artery pressure; GOLD: Global Initiative for Chronic Obstructive Lung Disease; sPAP: systolic pulmonary artery pressure; PAOP: pulmonary artery occlusion pressure; FEV₁: forced expiratory volume in 1 second; % pred: % predicted; PAP: pulmonary artery pressure; IPAH: idiopathic pulmonary arterial hypertension; TTPG: trans-tricuspid pressure gradient; TR: tricuspid regurgitant; K_{CO}: transfer coefficient of the lung for carbon monoxide; D_{LOO}: diffusing capacity of the lung for carbon monoxide; VC: vital capacity; PVR: pulmonary vascular resistance.

multiple aetiologies are involved, including vascular remodelling, endothelial dysfunction, inflammatory changes, alterations in pulmonary mechanics and host genetic factors (fig. 3). PH seems to be able to complicate COPD with any CT phenotypic expression of the disease (fig. 4).

Vascular remodelling

It was widely believed that alveolar hypoxia leading to pulmonary vasoconstriction and subsequent vascular remodelling was the primary aetiology for the development of PH in COPD. This theory was supported by the 1965 study by Hicken and colleagues: they noted vascular changes in patients with COPD and right ventricular hypertrophy that were similar to those seen in PH due to high altitude [29]. The inability of oxygen therapy to normalise pulmonary pressure seemed to support the concept that hypoxaemia led to the irreversible vascular changes responsible for increased PVR [30]. Numerous studies of the pulmonary vasculature of patients with moderate-to-severe COPD have demonstrated both intimal and medial thickening of small muscular arterioles [31–33]. It is hypothesised that this thickening of arterioles leads to decreased compliance and higher resistance to flow [32]. Some theorise that these structural changes may be due to the effects of cigarette smoke rather than hypoxaemia, as they can also be found in patients with mild, normoxaemic COPD and heavy smokers with normal lung function [34, 35].

Inflammation

Inflammation is a key component of the pathogenesis of

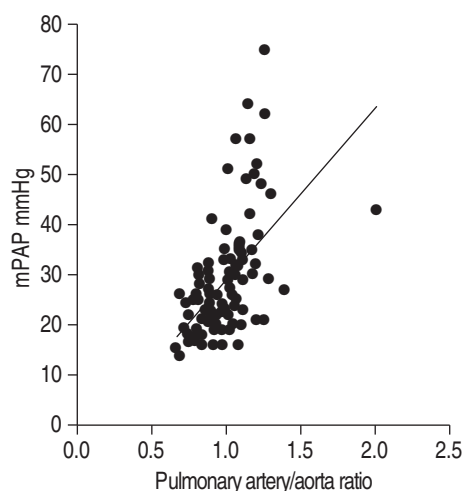


Figure 2. Pulmonary artery to aorta diameter ratio *versus* mean pulmonary artery pressure (mPAP).

COPD and may also contribute to the development of PH. Both smokers and patients with COPD have been found to have an increased number of inflammatory cells in the adventitia of the pulmonary arterioles, consisting primarily of CD8+ T-lymphocytes [36]. It is believed that inflammatory cells may play a role in the remodelling of pulmonary vessels. In fact, the severity of inflammation in small airways has been correlated with the degree of vascular remodelling [37, 38]. Additional support for the contribution of inflammation in the pathogenesis of PH is found in studies linking levels of inflammatory cytokines, including C-reactive protein (CRP), tumour necrosis factor (TNF)- α and interleukin (IL)-6 to elevated PAPs in COPD [39, 40].

Endothelial dysfunction

Endothelial cells in pulmonary vessels modulate vascular tone in response to hypoxaemia and changes in blood flow. This is accomplished through the release of vasodilatory mediators such as nitric oxide (NO), prostacyclin and vasoconstrictive mediators, including endothelin-1 (ET-1) and angiotensin. Disruption of this delicate balance can result in vascular remodelling and aberrant vascular physiology [41]. Endothelial NO synthase (eNOS) expression has been demonstrated to

be reduced in both primary and secondary PH, suggesting that downregulation of NO may have a causative role in the development of PH [42, 43]. The expression of eNOS has also been shown to be reduced in smokers and those with COPD [6, 44]. Studies have found decreased expression of prostacyclin synthase in severe COPD [45] as well as in patients with severe PH [46], suggesting a possible mechanistic link between decreased prostacyclin expression and the development of PH. Finally, increased expression of ET-1 has been exhibited in both primary and secondary forms of PH [47].

Alterations in pulmonary function

mPAP is equal to the sum of pulmonary capillary wedge pressure and the product of PVR and cardiac output. Thus, increases in any of these variables can increase mPAP [48]. A relatively high proportion of patients with COPD

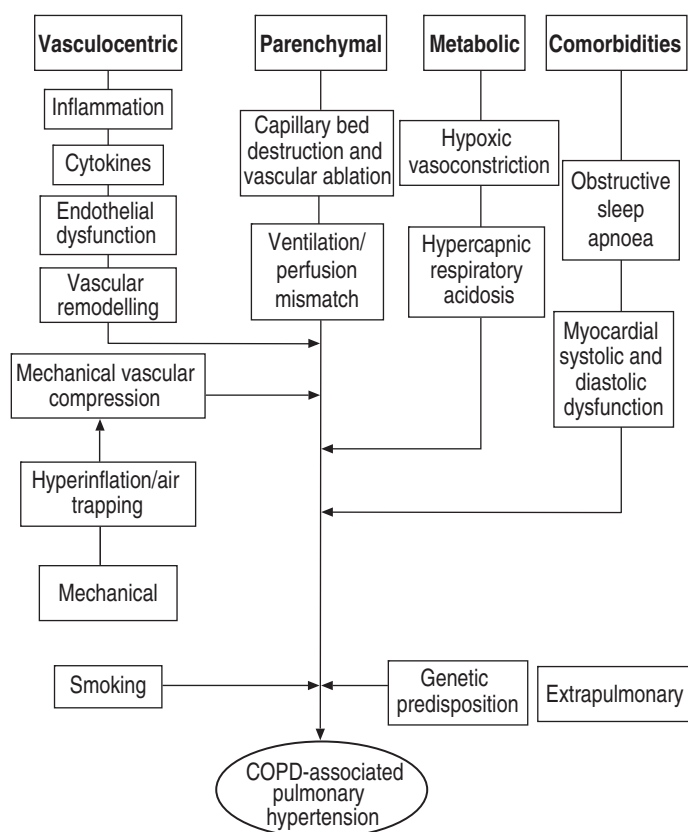


Figure 3. Flow diagram of the potential pathophysiological mechanisms of pulmonary hypertension in COPD.

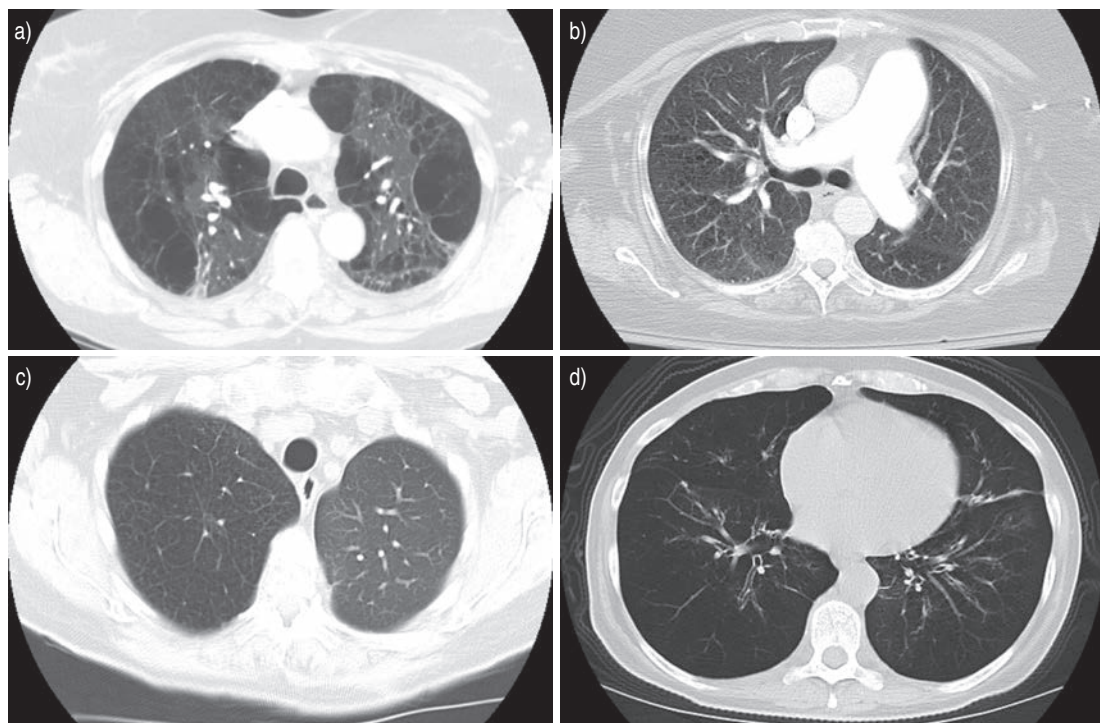


Figure 4. Computed tomography of COPD phenotypes and associated pulmonary hypertension. a) Forced expiratory volume in 1 second (FEV₁) 64% predicted, FEV₁/forced vital capacity (FVC) 59%, mean pulmonary artery pressure (mPAP) 25 mmHg. b) FEV₁ 44% pred, FEV₁/FVC 59%, mPAP 75 mmHg. c) FEV₁ 23% pred, FEV₁/FVC 57%, mPAP 48 mmHg. d) FEV₁ 13% pred, FEV₁/FVC 28%, mPAP 32 mmHg.

(19%) have been shown to have an increased pulmonary capillary wedge pressure at rest [49]. While this finding may be due primarily to left heart disease, it has been proposed that hyperinflation, with transmission of the associated increased intrathoracic pressure to the pulmonary vasculature, could also be responsible. Dynamic hyperinflation with exercise could exacerbate this phenomenon but the relative contribution of this putative mechanism remains unclear. PH was not demonstrated to improve after LVRS, which would be expected to improve air trapping and thus decrease intrathoracic pressure. It could be hypothesised that while alleviation of hyperinflation did result in reduced pulmonary pressures, this could have been counterbalanced by the removal of some of the pulmonary vascular reserve, with the net result being no change in the PAP [50].

Genetic factors

Multiple genetic polymorphisms have been associated with the development of PH in COPD. Serotonin is involved in pulmonary artery smooth muscle cell proliferation and vascular remodelling [51]. L allelic polymorphisms lead to overexpression of the serotonin transporter (5-HTT). LL 5-HTT gene expression correlates with the severity of PH in COPD [51, 52]. The angiotensin-converting enzyme (ACE) gene contains a polymorphism based on the insertion (I) or deletion (D) of a nonsense DNA domain, and can result in three distinct genotypes: DD, DI or II [53]. The DI genotype may confer susceptibility to PH evoked by exercise [54] and may be linked to the development of PH in Caucasians with COPD [55]. The IL-6 GG genotype and BB polymorphism of the eNOS gene have also been associated with the development of PH in COPD [40, 56]. It is possible that in the future, genetic screening of patients with COPD will facilitate early monitoring for the development of, and perhaps therapy to prevent, PH.

Out-of-proportion PH

The mechanisms responsible for “out-of-proportion” PH in COPD are poorly understood. It is unclear whether it represents a severe variant of COPD-associated PH caused by the same mechanisms or a distinct clinical entity. One theory is that these patients are “high responders” to acute hypoxaemia, perhaps due to a genetic predisposition. Another possibility is that out-of-proportion PH is a separate disease similar to idiopathic PAH [57]. Given the current uncertainty and poor prognosis associated with this clinical variant, it is imperative that clinicians identify such patients so that they can be enrolled in clinical trials to further our understanding of this phenomenon.

How out-of-proportion PH should be defined is as yet unknown and remains controversial. It has been suggested that it can be defined as an mPAP cut-off of either >35 or >40 mmHg [48]; this, however, is yet to be validated. What, then, should be the standard against which the presence or absence of out-of-proportion PH is judged? There are several conceptual frameworks whereby this might be defined. If one were to define it as the level of PH that drives mortality, then any PH in the context of COPD would be out of proportion, as any element of pressure increase appears to impact survival. If patients have a cardiovascular rather than a ventilatory limitation to exercise, then this perhaps should define those with out-of-proportion PH. However, discerning these two forms of exercise limitation can be difficult, even with formal cardiopulmonary exercise testing. Alternatively, it might only be possible to define this in retrospect according to those patients who demonstrate an objective response to therapies directed at their PH. In order to recognise it in the initial stages, however, rather than as a rigid cut-point, a variable or adaptive threshold might be warranted in which the mPAP cut-point is evaluated in the context of the patient’s lung function. Specifically, the greater the FEV₁, the lower the cut-point, and conversely the lower the FEV₁ (hence, a greater likelihood of a ventilatory limitation), the higher the mPAP threshold to define out-of-proportion PH. Conceptual examples of this adaptive approach may be a mPAP threshold >25 mmHg for those patients with FEV₁ of 50% or greater and a mPAP threshold of >50 mmHg for those with FEV₁ $<25\%$ pred. An example of this hypothetical concept is further illustrated by the shaded area in figure 5.

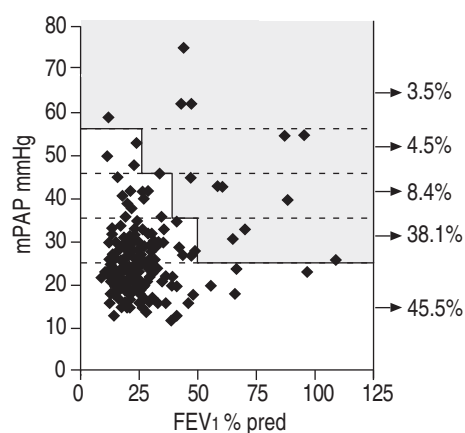


Figure 5. Forced expiratory volume in 1 second (FEV₁) versus mean pulmonary artery pressure (mPAP). The shaded area represents the concept of a variable FEV₁ to mPAP relationship, which might define “out-of-proportion” pulmonary hypertension. $n=190$. % pred: % predicted.

Diagnosis

Establishing a diagnosis of PH, particularly in the small percentage of COPD patients with severe or out-of-proportion PH, can have important prognostic and potentially therapeutic implications. However, diagnosis can be difficult in the COPD population, where the symptoms of PH overlap broadly with symptoms of obstructive lung disease itself. Furthermore, the hyperinflation that is characteristic of COPD can impede common diagnostic modalities, including physical examination and echocardiography.

Initial evaluation

Perhaps the most important component of PH evaluation in COPD patients is a thorough history to exclude other, more common causes of PH. These include left ventricular dysfunction, obstructive sleep apnoea, thromboembolic disease, associated pulmonary fibrosis, an underlying connective tissue disease,

and anorexigen use. In a previous study, only 11 out of 27 patients with COPD and severe PH (mPAP >40 mmHg) had no other potential explanation for their PH [18]. Therefore, COPD patients with significant PH warrant a thorough evaluation for other aetiologies before the cause is attributed to underlying COPD alone.

Physical examination findings of PH, such as right ventricular heave and a prominent S₂ heart sound, are not sensitive and may be further obscured by lung hyperinflation. As most of the PH in COPD tends to be mild to moderate, features of cor pulmonale are unusual and only occur late in the disease course of those patients with more severe PH. Likewise, ECG findings such as p pulmonale, incomplete right bundle branch block or right ventricular hypertrophy are also insensitive for the diagnosis of PH [9]. However, ECG findings may have reasonable specificity and should prompt consideration of a further evaluation for PH.

Spirometry

Abnormal spirometry is inherent to the diagnosis of COPD. In the study by CHAOUAT *et al.* [18], patients with severe PH tended to have less severe obstruction and a lower diffusing capacity of the lung for carbon monoxide (*DL*_{CO}). These patients also had more prominent hypoxaemia and hypocapnia, and severe exertional dyspnoea. Therefore, the presence of PH is suggested in COPD patients with dyspnoea, hypoxaemia or functional limitation that appears out of proportion with spirometric abnormalities.

Biomarkers

Serum brain natriuretic peptide (BNP) is elevated in both COPD and PAH, and is associated with a worse prognosis and decreased time to exacerbation in COPD [58]. In a mixed population with chronic lung disease, approximately 25% of whom had COPD, elevated serum BNP predicted underlying PH with a sensitivity and specificity of 85% and 88%, respectively [59]. Another study showed that an N-terminal proBNP (NT-proBNP) of <95 pg·mL⁻¹ excluded PH by echocardiogram, with a 100% negative predictive value [60]. Larger studies to further define the role of serum BNP as a screening test for PH in COPD are nonetheless still required.

Imaging

Increased size of the pulmonary artery on thoracic CT has previously been shown to be an indicator of PH [61]. Various indicators on both chest radiograph and CT have been suggested as predictors of PH [62, 63]. Using advanced software, MATSUOKA *et al.* [64] showed that vascular alteration on high-resolution CT (HRCT) (specifically, a decrease in the cross-sectional area of small (<5 mm) pulmonary vessels) correlated with mPAP. In their study, pulmonary artery size and the pulmonary artery/aortic diameter ratio did not correlate with pulmonary pressure. In general, no radiological criterion has significant sensitivity or specificity to serve as a stand-alone test for PH. The findings of WELLS *et al.* [28], however, are clinically significant. They recently showed that an increased pulmonary artery size, as indicated by a main pulmonary artery diameter/aortic diameter ratio of greater than 1.0, was associated with severe exacerbations of COPD. Although PH was previously known to be associated with exacerbations and a worse prognosis in COPD, this simple indicator readily identifies high-risk patients without a direct diagnosis of PH, and may have significant future treatment implications.

Echocardiography

Echocardiographic assessment of the tricuspid regurgitant jet to estimate pulmonary pressures is frequently used as a noninvasive surrogate for the measurement of pulmonary pressures by RHC. However, this technique has several pitfalls. Specifically, the tricuspid regurgitant jet may not be adequately visualised, particularly in COPD patients with hyperinflated lungs. In one study of advanced lung disease patients, sPAP could not be estimated in over 50% of patients [65]. Use of

echocardiographic contrast material may improve visualisation and enable the assessment of PAP [66]. There is also some evidence that other echocardiographic techniques may improve the ability to estimate PAP. Using Doppler analysis of jugular venous flow velocity, one group was able to obtain a reliable echocardiographic window in all patients, as compared with 87% for the assessment of pulmonary artery acceleration and ejection times, and only 55% for the assessment of the tricuspid regurgitant jet [67].

It is perhaps of greater concern that values derived from echocardiography may both over- and underestimate sPAP compared with RHC. In the Arcasoy study, in those in whom sPAP could be estimated by echocardiography, 48% were misclassified as having PH. A subset of COPD patients from the National Emphysema Treatment Trial (NETT) demonstrated echocardiography to be a poor predictor of PH, with positive and negative predictive values of only 68% and 67%, respectively [68]. A formula incorporating the pulmonary artery/aorta diameter ratio by CT and right ventricular systolic pressure by echocardiography has been assessed; it is possible that this method predicts PH more accurately than either CT or echocardiography alone, although few patients with COPD were studied [69]. Therefore, although noninvasive testing, including echocardiography, has a clear role in PH screening in COPD, the definitive diagnosis continues to require invasive haemodynamic measurements.

Right heart catheterisation

PH, whether secondary to COPD or from other causes, requires RHC for a definitive diagnosis. In addition to quantification of pulmonary pressures, PH secondary to cardiac systolic or diastolic dysfunction can also be excluded. RHC is not recommended for all COPD patients due to the cost and invasive nature of the procedure. RHC is recommended in patients who are being considered for surgical interventions, including LVRS or lung transplantation, or in those in whom there is a high suspicion of out-of-proportion PH, where this information is deemed to be important [70].

Treatment

Oxygen therapy is the only universally accepted treatment for PH in COPD patients with confirmed hypoxia. Stabilisation of pulmonary pressure as well as decreased mortality over time have been demonstrated and are well accepted in this population [71, 72]. The role of other treatments, particularly pulmonary vasodilator therapy, is less clear in patients with COPD complicated by PH. Table 2 summarises data regarding specific treatments for PH in COPD.

Oxygen therapy

A longitudinal study of 16 patients with COPD, who had serial RHC data over time, investigated the natural history of PH in COPD and the impact of long-term oxygen therapy on pulmonary haemodynamics. Before the institution of oxygen therapy in this group, mean $\pm$ SD mPAP increased from 23.3 ± 6.8 to 28.0 ± 7.4 mmHg ($p < 0.005$), whereas P_{a,O_2} decreased from 59.3 to 50.2 mmHg over an average follow-up interval of 47 months. Following the institution of oxygen therapy for 15–18 hours per day, RHC was again repeated (average follow-up interval 31 ± 19 months) and revealed a significant improvement in mPAP (from 28.0 ± 7.4 to 23.9 ± 6.6 mmHg, $p < 0.005$) and PVR. PH improved in 12 of the 16 patients. There were no significant differences in pulmonary capillary wedge pressure, cardiac output or P_{a,O_2} following the initiation of oxygen therapy. The study suggests that long-term oxygen therapy for 15–18 hours per day can improve pulmonary pressure in a large percentage of patients; without it, progression of PH over time is likely to occur [80].

In a larger 6-year prospective study, the long-term effects of 14–15 hours per day oxygen therapy on pulmonary haemodynamics in patients with severe COPD and hypoxaemia were studied. Baseline hemodynamic measurements by RHC revealed mPAP of 28 ± 11 mmHg in the 95 COPD patients

studied. After 2 years of supplemental oxygen therapy, a subset of 39 patients agreed to repeat RHC and were found to have a small decrease in mPAP from 25 ± 8 to 23 ± 6 mmHg (not statistically significant) despite worsening hypoxaemia (P_{a,O_2} 59 ± 8 versus 53 ± 8 mmHg, $p < 0.05$). In 12 patients in whom follow-up haemodynamic data were obtained for 6 years, there was a small reduction in PH at 2 years followed by stabilisation over the next 4 years (25 ± 7 , 21 ± 4 , 26 ± 7 and 26 ± 6 mmHg at 2, 4 and 6 years, respectively), despite continued progression of airway obstruction and hypoxaemia. These data confirmed that long-term oxygen therapy may mitigate the progression of PH over time in the face of worsening COPD [81].

Nitric oxide

The role of inhaled NO as a pulmonary vasodilator in combination with oxygen therapy was investigated in a group of severe COPD patients. In the study, 40 patients with PH and COPD received either oxygen alone or “pulsed” inhalation of NO and oxygen for 3 months. Following treatment, there was a significant reduction in mPAP in the NO group compared with oxygen therapy alone (from 27.6 to 20.6 mmHg versus 24.6 to 25.2 mmHg, $p < 0.001$). Likewise, there was a significant improvement in PVR and cardiac output in the NO group. There was no evidence of worsening arterial oxygenation or toxic reaction products from the NO [73].

Table 2. Published studies on the treatment of pulmonary hypertension in COPD

First author [ref.]	Subjects n	GOLD stage	Baseline mPAP mmHg	Study design	Therapy	Outcome
VONBANK [73]	40	II–IV	26 ± 5	Randomised controlled trial	“Pulsed” nitric oxide with oxygen versus oxygen alone for 3 months	Improved haemodynamics without worsened hypoxaemia
RIETEMA [74]	15	II–IV	22 ± 9 at rest, 32 ± 11 with exercise	Prospective, single arm	Sildenafil 50 mg <i>t.i.d.</i> for 12 weeks	No change in 6MWD, CPET or stroke volume
STOLZ [75]	30	III–IV	No RHC data; sPAP	Randomised controlled trial (2:1)	Bosentan 125 mg <i>b.i.d.</i> for 12 weeks [#]	No change in 6MWD, worsened hypoxaemia and health-related quality of life
BLANCO [76]	20	III–IV	34 mmHg by echo 27 ± 10	Dose comparison trial	Single dose of sildenafil 20 mg or 40 mg	Improvement in haemodynamics, worsened hypoxaemia at rest
HEGEWALD [77]	1	II	74	Case report	Inhaled iloprost 5 µg six times daily for 2 years	Improved haemodynamics, 6MWD and functional class
PARK [78]	23	III–IV	No RHC data; sPAP 36 mmHg by echo	Prospective, single arm	Udenafil 50 mg daily for 8 weeks	Improved 6MWD and decreased sPAP
DUMAS DE LA ROQUE [79]	8	III–IV	26 (25–27)	Case series	DHEA 200 mg daily for 3 months	Improved 6MWD and pulmonary haemodynamics without worsened hypoxaemia

Data are presented as mean $\pm$ sd and median (interquartile range). GOLD: Global Initiative for Chronic Obstructive Lung Disease; mPAP: mean pulmonary artery pressure; 6MWD: 6-minute walk distance; CPET: cardiopulmonary exercise testing; RHC: right heart catheterisation; sPAP: systolic pulmonary artery pressure; echo: echocardiography; DHEA: dehydroepiandrosterone. [#]: initial dose of 62.5 mg orally *b.i.d.* for 2 weeks then increased to 125 mg orally *b.i.d.* for the remainder of the study.

Phosphodiesterase-5 inhibitor therapy

The effects of sildenafil on stroke volume and exercise capacity were investigated in 15 stable Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II–IV COPD patients over a 3-month time period. These patients underwent RHC at baseline, which revealed mPAP of 22 ± 9 mmHg at rest and 32 ± 11 mmHg with exercise. Of the 15 patients, five (33%) had PH at rest (mPAP ≥ 25 mmHg) while an additional four (26.7%) had PH during exercise (mPAP ≥ 30 mmHg). Stroke volume was lower in COPD patients compared with healthy controls, and this difference was even more pronounced during exercise. After 12 weeks of oral therapy with sildenafil 50 mg three times daily, there was no improvement in exercise capacity as measured by the 6-minute walk distance and cardiopulmonary exercise testing. Stroke volume also did not change following treatment [74].

A dose comparison trial of sildenafil was performed to investigate the haemodynamics and gas exchange effects, including ventilation/perfusion (V'/Q') relationships, of a single dose of sildenafil (20 mg or 40 mg) in 20 patients with severe COPD and a mean FEV₁ of 35% pred. At RHC, 17 were found to have PH at rest (mPAP >20 mmHg) and three had exercise-induced PH (mPAP >30 mmHg). Of the 20 patients, 11 were assigned to 20 mg of sildenafil therapy administered as a single dose and nine were assigned to 40 mg. Haemodynamic, gas exchange and spirometric measurements were performed at baseline and then repeated 1 hour post treatment. Both sildenafil doses resulted in a reduction of mPAP both at rest (-6 mmHg) and with exercise (-11 mmHg) by RHC. At rest with both doses, there was a 6-mmHg reduction in P_{a,O_2} (95% CI -8 to -4 mmHg), which was accompanied by, and presumably attributable to, increased perfusion in areas of the lung with a reduced V'/Q' ratio. However, with exercise, no significant changes in P_{a,O_2} or V'/Q' relationships were observed after sildenafil dosing [76].

More recently, a Korean group of investigators studied the effects of treatment with udenafil, another phosphodiesterase-5 inhibitor, in 23 severe COPD patients with a median FEV₁ of 35% pred. After 8 weeks of udenafil 50 mg daily, 6-minute walk distance improved from 315 m to 348 m ($p=0.03$) and the median sPAP estimate by echocardiography decreased from 36 mmHg to 30 mmHg ($p=0.02$). There were no differences in the St George's Respiratory Questionnaire (SGRQ) score, the Borg dyspnoea score or spirometry. The dropout rate was significant, with nine (26.4%) of patients discontinuing therapy due to adverse events, including worsening dyspnoea (three patients), flushing (two patients), dizziness (two patients), and palpitations (two patients) [78].

Endothelin-receptor antagonist therapy

The effects of bosentan were studied in a randomised controlled trial of 30 patients with GOLD stage III–IV COPD. Notably, inclusion in the study was not contingent upon the presence of PH. In fact, no RHC data were assessed in the study and echocardiographic evidence of PH was only present in 20 of the 30 patients, with a mean estimated sPAP at rest of 37 mmHg in the placebo group *versus* 32 mmHg in the treatment group ($p=0.779$). After 12 weeks of treatment, patients treated with bosentan showed no improvement in 6-minute walk distance compared with patients in the placebo arm (mean difference of -10 *versus* 0 m, $p=0.474$). There were no significant differences between the two groups with regard to secondary end-points, including lung function, maximal oxygen uptake during cardiopulmonary exercise testing, estimated PAP at rest or Borg dyspnoea index. P_{a,O_2} decreased in the bosentan group over the course of the study compared with the placebo group, as did health-related quality of life. Overall, this study provides evidence that treatment with endothelin-receptor antagonist therapy in severe COPD patients without severe PH is detrimental to both oxygenation and functional status [75].

Prostanoid therapy

Inhaled iloprost has been reported to have been used successfully in the treatment of a COPD patient with GOLD stage II disease (FEV₁ 52% pred) and severe PH (mPAP 74 mmHg). After

2 years of therapy with 5 µg inhaled iloprost six times per day, the patient showed improvements in haemodynamics (mPAP decreased to 67 mmHg with a concomitant increase in cardiac output), 6-minute walk test distance and WHO functional class (decreased from IV to II). The authors of this single case report hypothesised that in a subset of COPD patients with disproportionately severe PH (mPAP >40 mmHg), inhaled prostanoid therapy may preferentially vasodilate regions of the lung that are well ventilated, resulting in reduced V'/Q' mismatch and arterial hypoxaemia in comparison with other systemic pulmonary vasodilators [77].

Dehydroepiandrosterone

Animal studies have previously demonstrated that dehydroepiandrosterone (DHEA), an endogenous steroid produced in the adrenal glands, reverses chronic hypoxia-induced PH in rats [79]. On this basis, a human study was conducted to investigate whether DHEA can improve the clinical and haemodynamic status of patients with PH associated with COPD. Eight patients with PH associated with COPD were treated with DHEA at a dose of 200 mg daily for 3 months. After 3 months of treatment, the median 6-minute walk distance of the group increased from 333 to 390 m ($p<0.05$); the Borg index did not improve. Haemodynamics measured by RHC showed an improvement in mPAP (from 26 to 21 mmHg, $p<0.05$) and PVR (from 4.2 to 2.6 IU). Cardiac output and pulmonary capillary wedge pressure did not change significantly before and after treatment [79].

Conclusion

In summary, oxygen therapy is recommended as a treatment for PH associated with COPD. The role of pharmacotherapy in patients with COPD-associated PH remains unresolved and controversial. The small studies performed to date are encouraging and suggest that there is a potential role for such a therapeutic approach. However, before pulmonary vasoactive agents can be universally endorsed as a therapy in COPD-associated PH, the appropriate phase III randomised controlled trials need to be successfully completed. The design of these studies (specifically, the inclusion and exclusion criteria) will be critical to their success. It is likely that not all COPD PH patients will demonstrate a short- or medium-term response to therapy and it might only be a small subset of severe patients (~7%) with out-of-proportion PH who benefit from a functional standpoint. It will also be important in the context of these studies to exclude patients who are likely to be harmed, specifically those who might be predisposed to worsened V'/Q' matching and hypoxaemia. In this regard, an adaptive study design might enable such patients to be excluded almost straightaway after a test dose or test period, to ensure no such untoward side-effects occur, prior to randomisation. If a survival end-point is considered for a phase III therapeutic study, then it might be reasonable to include all patients with COPD-associated PH; after all, the original oxygen therapy trials, in which a mortality benefit was demonstrated, were performed in broad groups of COPD patients and mechanistically it is likely that amelioration of PH played a role in the positive outcomes demonstrated [71]. When such studies become available, COPD patients with PH should be referred on for enrolment.

However, what are clinicians to do in the interim with these patients? It seems reasonable to consider therapy in COPD patients whose PH is out of proportion with their underlying obstructive disease. If therapy is being considered, it is crucial that patients participate in this decision and are informed of the lack of data and potential risks, as well as the hoped-for benefits. Goals and duration of therapy should be determined *a priori*; if there is no documented objective evidence of improvement or if there is evidence of harm on close follow-up, therapy should be discontinued.

Practicing medicine in a vacuum of data runs the risk of potentially harmful therapies becoming accepted as standard care. A recent example of this is the endorsement of azathioprine steroid therapy for idiopathic pulmonary fibrosis (IPF) in a consensus statement from 2000 [82]; such

treatment was recently shown to be harmful in the context of the appropriate randomised controlled trial [83]. COPD has been estimated to affect 9% of individuals >40 years of age, which approximates to 216 million individuals worldwide suffering from this disease [84]. Some of these patients are likely to die with their COPD rather than from their COPD. Even if one were to take a conservative approach and assume that 50 million of these patients advanced to the point that they might be predisposed to complicating PH, and assuming a prevalence of disproportionate PH of 1–7%, then the burden of potentially treatable PH might number 500,000–3.5 million patients. If the concept of treating PH in the context of COPD proves true, the societal benefits and reduction in healthcare costs could be enormous for a disease whose prevalence and mortality burden continue to increase. A concerted, coordinated effort by pharmaceutical companies, governmental agencies and clinical researchers is strongly encouraged to fund and implement these necessary studies.

Support Statement

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Dept of the Army, Dept of Defence, or the US Government.

Statement of Interest

S.D. Nathan has received research funding and educational grants, has been a consultant for and is on the speakers' bureau of Actelion, Gilead Sciences and United Therapeutics.

References

- Andersen KH, Iversen M, Kjaergaard J, *et al.* Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2012; 31: 373–380.
- Weitzenblum E, Hirth C, Ducolone A, *et al.* Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981; 36: 752–758.
- Weitzenblum E, Sautegau A, Ehrhart M, *et al.* Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984; 130: 993–998.
- Kessler R, Faller M, Weitzenblum E, *et al.* “Natural history” of pulmonary hypertension in a series of 131 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 219–224.
- Burrows B, Kettel LJ, Niden AH, *et al.* Patterns of cardiovascular dysfunction in chronic obstructive lung disease. *N Engl J Med* 1972; 286: 912–918.
- Barbera JA, Blanco I. Pulmonary hypertension in patients with chronic obstructive pulmonary disease: advances in pathophysiology and management. *Drugs* 2009; 69: 1153–1171.
- Minai OA, Chaouat A, Adnot S. Pulmonary hypertension in COPD: epidemiology, significance, and management: pulmonary vascular disease: the global perspective. *Chest* 2010; 137: 39S–51S.
- Scharf SM, Iqbal M, Keller C, *et al.* Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med* 2002; 166: 314–322.
- Oswald-Mammoser M, Oswald T, Nyankiye E, *et al.* Non-invasive diagnosis of pulmonary hypertension in chronic obstructive pulmonary disease. Comparison of ECG, radiological measurements, echocardiography and myocardial scintigraphy. *Eur J Respir Dis* 1987; 71: 419–429.
- Badesch DB, Champion HC, Sanchez MA, *et al.* Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: S55–S66.
- Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: S43–S54.
- McGoon MD. The assessment of pulmonary hypertension. *Clin Chest Med* 2001; 22, 493–508: ix.
- Fisher MR, Forfia PR, Chamera E, *et al.* Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009; 179: 615–621.
- Rich JD, Shah SJ, Swamy RS, *et al.* Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. *Chest* 2011; 139: 988–993.
- Mykland Hilde J, Skjorten I, Hansteen V, *et al.* Hemodynamic responses to exercise in patients with COPD. *Eur Respir J* 2012; [Epub ahead of print DOI: 10.1183/09031936.00085612].
- Gartman EJ, Blundin M, Klinger JR, *et al.* Initial risk assessment for pulmonary hypertension in patients with COPD. *Lung* 2012; 190: 83–89.
- Thabut G, Dauriat G, Stern JB, *et al.* Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 2005; 127: 1531–1536.
- Chaouat A, Bugnet AS, Kadaoui N, *et al.* Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 189–194.

19. Fayngersh V, Drakopanagiotakis F, McCool FD, *et al.* Pulmonary hypertension in a stable community-based COPD population. *Lung* 2011; 189: 377–382.
20. Sertogullarindan B, Gumrukcuoglu HA, Sezgi C, *et al.* Frequency of pulmonary hypertension in patients with COPD due to biomass smoke and tobacco smoke. *Int J Med Sci* 2012; 9: 406–412.
21. Cuttica MJ, Kalhan R, Shlobin OA, *et al.* Categorization and impact of pulmonary hypertension in patients with advanced COPD. *Respir Med* 2010; 104: 1877–1882.
22. Higham MA, Dawson D, Joshi J, *et al.* Utility of echocardiography in assessment of pulmonary hypertension secondary to COPD. *Eur Respir J* 2001; 17: 350–355.
23. Oswald-Mammossier M, Weitzenblum E, Quoix E, *et al.* Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest* 1995; 107: 1193–1198.
24. Doi M, Nakano K, Hiramoto T, *et al.* Significance of pulmonary artery pressure in emphysema patients with mild-to-moderate hypoxemia. *Respir Med* 2003; 97: 915–920.
25. Wuertemberger G, Zielinsky J, Sliwinsky P, *et al.* Survival in chronic obstructive pulmonary disease after diagnosis of pulmonary hypertension related to long-term oxygen therapy. *Lung* 1990; 168: Suppl. 762–769.
26. Celli BR, Cote CG, Marin JM, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
27. Christensen CC, Ryg MS, Edvardsen A, *et al.* Relationship between exercise desaturation and pulmonary haemodynamics in COPD patients. *Eur Respir J* 2004; 24: 580–586.
28. Wells JM, Washko GR, Han MK, *et al.* Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med* 2012; 367: 913–921.
29. Hicken P, Heath D, Brewer DB, *et al.* The small pulmonary arteries in emphysema. *J Pathol Bacteriol* 1965; 90: 107–114.
30. Abraham AS, Cole RB, Bishop JM. Reversal of pulmonary hypertension by prolonged oxygen administration to patients with chronic bronchitis. *Circ Res* 1968; 23: 147–157.
31. Wilkinson M, Langhorne CA, Heath D, *et al.* A pathophysiological study of 10 cases of hypoxic cor pulmonale. *Q J Med* 1988; 66: 65–85.
32. Magee F, Wright JL, Wiggs BR, *et al.* Pulmonary vascular structure and function in chronic obstructive pulmonary disease. *Thorax* 1988; 43: 183–189.
33. Wright JL, Petty T, Thurlbeck WM. Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial. *Lung* 1992; 170: 109–124.
34. Santos S, Peinado VI, Ramirez J, *et al.* Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J* 2002; 19: 632–638.
35. MacNee W. Right heart function in COPD. *Semin Respir Crit Care Med* 2010; 31: 295–312.
36. Peinado VI, Barbera JA, Abate P, *et al.* Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 1605–1611.
37. Barbera JA, Riverola A, Roca J, *et al.* Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994; 149: 423–429.
38. Hale KA, Ewing SL, Gosnell BA, *et al.* Lung disease in long-term cigarette smokers with and without chronic airflow obstruction. *Am Rev Respir Dis* 1984; 130: 716–721.
39. Joppa P, Petrasova D, Stancak B, *et al.* Systemic inflammation in patients with COPD and pulmonary hypertension. *Chest* 2006; 130: 326–333.
40. Chaouat A, Savale L, Chouaid C, *et al.* Role for interleukin-6 in COPD-related pulmonary hypertension. *Chest* 2009; 136: 678–687.
41. Wright JL, Levy RD, Churg A. Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications for treatment. *Thorax* 2005; 60: 605–609.
42. Peinado VI, Pizarro S, Barbera JA. Pulmonary vascular involvement in COPD. *Chest* 2008; 134: 808–814.
43. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995; 333: 214–221.
44. Barbera JA, Peinado VI, Santos S, *et al.* Reduced expression of endothelial nitric oxide synthase in pulmonary arteries of smokers. *Am J Respir Crit Care Med* 2001; 164: 709–713.
45. Nana-Sinkam SP, Lee JD, Sotto-Santiago S, *et al.* Prostacyclin prevents pulmonary endothelial cell apoptosis induced by cigarette smoke. *Am J Respir Crit Care Med* 2007; 175: 676–685.
46. Tudor RM, Cool CD, Geraci MW, *et al.* Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999; 159: 1925–1932.
47. Giaid A, Yanagisawa M, Langleben D, *et al.* Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993; 328: 1732–1739.
48. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32: 1371–1385.
49. Chabot F, Schrijen F, Poincelot F, *et al.* Interpretation of high wedge pressure on exercise in patients with chronic obstructive pulmonary disease. *Cardiology* 2001; 95: 139–145.
50. Haniuda M, Kubo K, Fujimoto K, *et al.* Effects of pulmonary artery remodeling on pulmonary circulation after lung volume reduction surgery. *Thorac Cardiovasc Surg* 2003; 51: 154–158.

51. Shujaat A, Minkin R, Eden E. Pulmonary hypertension and chronic cor pulmonale in COPD. *Int J Chron Obstruct Pulmon Dis* 2007; 2: 273–282.
52. Eddahibi S, Chaouat A, Morrell N, *et al.* Polymorphism of the serotonin transporter gene and pulmonary hypertension in chronic obstructive pulmonary disease. *Circulation* 2003; 108: 1839–1844.
53. Elwing J, Panos RJ. Pulmonary hypertension associated with COPD. *Int J Chron Obstruct Pulmon Dis* 2008; 3: 55–70.
54. Kanazawa H, Okamoto T, Hirata K, *et al.* Deletion polymorphisms in the angiotensin converting enzyme gene are associated with pulmonary hypertension evoked by exercise challenge in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1235–1238.
55. Tkacova R, Joppa P, Stancak B, *et al.* The link between angiotensin-converting enzyme genotype and pulmonary artery pressure in patients with COPD. *Wiener klinische Wochenschrift* 2005; 117: 210–214.
56. Yildiz P, Oflaz H, Cine N, *et al.* Gene polymorphisms of endothelial nitric oxide synthase enzyme associated with pulmonary hypertension in patients with COPD. *Respir Med* 2003; 97: 1282–1288.
57. Weitzenblum E, Chaouat A. Severe pulmonary hypertension in COPD: is it a distinct disease? *Chest* 2005; 127: 1480–1482.
58. Inoue Y, Kawayama T, Iwanaga T, *et al.* High plasma brain natriuretic peptide levels in stable COPD without pulmonary hypertension or cor pulmonale. *Intern Med* 2009; 48: 503–512.
59. Leuchte HH, Baumgartner RA, Nounou ME, *et al.* Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med* 2006; 173: 744–750.
60. Andersen CU, Mellemejaer S, Nielsen-Kudsk JE, *et al.* Echocardiographic screening for pulmonary hypertension in stable COPD out-patients and NT-proBNP as a rule-out test. *COPD* 2012; 9: 505–512.
61. Ng CS, Wells AU, Padley SP. A CT sign of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. *J Thorac Imaging* 1999; 14: 270–278.
62. Lupi E, Dumont C, Tejada VM, *et al.* A radiologic index of pulmonary arterial hypertension. *Chest* 1975; 68: 28–31.
63. Edwards PD, Bull RK, Coulden R. CT measurement of main pulmonary artery diameter. *Br J Radiol* 1998; 71: 1018–1020.
64. Matsuoka S, Washko GR, Yamashiro T, *et al.* Pulmonary hypertension and computed tomography measurement of small pulmonary vessels in severe emphysema. *Am J Respir Crit Care Med* 2010; 181: 218–225.
65. Arcasoy SM, Christie JD, Ferrari VA, *et al.* Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003; 167: 735–740.
66. Himelman RB, Stulbarg M, Kircher B, *et al.* Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography in chronic pulmonary disease. *Circulation* 1989; 79: 863–871.
67. Matsuyama W, Ohkubo R, Michizono K, *et al.* Usefulness of transcutaneous Doppler jugular venous echo to predict pulmonary hypertension in COPD patients. *Eur Respir J* 2001; 17: 1128–1131.
68. Fisher MR, Criner GJ, Fishman AP, *et al.* Estimating pulmonary artery pressures by echocardiography in patients with emphysema. *Eur Respir J* 2007; 30: 914–921.
69. Devaraj A, Wells AU, Meister MG, *et al.* Detection of pulmonary hypertension with multidetector CT and echocardiography alone and in combination. *Radiology* 2010; 254: 609–616.
70. Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.
71. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93: 391–398.
72. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
73. Vonbank K, Ziesche R, Higenbottam TW, *et al.* Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax* 2003; 58: 289–293.
74. Rietema H, Holverda S, Bogaard HJ, *et al.* Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J* 2008; 31: 759–764.
75. Stolz D, Rasch H, Linka A, *et al.* A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J* 2008; 32: 619–628.
76. Blanco I, Gimeno E, Munoz PA, *et al.* Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med* 2010; 181: 270–278.
77. Hegewald MJ, Elliott CG. Sustained improvement with iloprost in a COPD patient with severe pulmonary hypertension. *Chest* 2009; 135: 536–537.
78. Park JS, Lim HJ, Cho YJ, *et al.* Udenafil improves exercise capacity in patients with chronic obstructive pulmonary disease: a prospective study. *COPD* 2012; 9: 499–504.
79. Dumas de La Roque E, Savineau JP, Metivier AC, *et al.* Dehydroepiandrosterone (DHEA) improves pulmonary hypertension in chronic obstructive pulmonary disease (COPD): a pilot study. *Ann Endocrinol* 2012; 73: 20–25.
80. Weitzenblum E, Sautegau A, Ehrhart M, *et al.* Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; 131: 493–498.

81. Zielinski J, Tobiasz M, Hawrylkiewicz I, *et al.* Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. *Chest* 1998; 113: 65–70.
82. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000; 161: 646–664.
83. Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; 366: 1968–1977.
84. Halbert RJ, Natoli JL, Gano A, *et al.* Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28: 523–532.

Chapter 15

COPD and thrombosis

Peter K. MacCallum



SUMMARY: Evidence has emerged over the past decade whereby COPD is characterised by changes in molecular markers that are consistent with a systemic inflammatory and prothrombotic state. These changes may in part explain the increasingly recognised associations between COPD and ischaemic heart disease, ischaemic stroke and venous thromboembolism, these clinical manifestations resulting from the pathological process of thrombosis that are collectively the leading causes of death worldwide. Alterations in these markers become more pronounced at the time of acute exacerbations, which are themselves associated with further increases in cardiovascular disease risk. Therefore, COPD provides an informative clinical model to study associations between inflammation, infection and thrombosis. Clinicians need to bear in mind the associations of COPD with both arterial and venous thrombotic disorders and adapt existing strategies for the prevention of such outcomes in their patients.

KEYWORDS: Cardiovascular disease, COPD, ischaemic heart disease, pulmonary embolism, venous thromboembolism

Correspondence: P.K. MacCallum,
The Wolfson Institute of Preventive
Medicine, Barts and The London
School of Medicine and Dentistry,
Queen Mary University of London,
Charterhouse Square, London, EC1M
6BQ, UK.
Email: p.k.maccallum@qmul.ac.uk

Eur Respir Monogr 2013; 59: 206–216.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10012512
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Thrombosis is the pathological process underlying most acute myocardial infarctions, ischaemic strokes and venous thromboembolism (VTE), comprising of deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Given the high incidence of these cardiovascular conditions and the seriousness of their consequences [2], it is no surprise that thrombosis is the most common pathological process causing mortality worldwide. Thrombosis is a multistep process, essentially involving interplay between activated cells (predominantly platelets) and the coagulation network, a regulated series of protein interactions that leads to the generation of thrombin and formation of fibrin [1]. Links between these components and the inflammatory system have been increasingly recognised over the past decade [3, 4] and may partly explain the associations between inflammation and cardiovascular diseases [5]. There is mounting evidence that platelets and coagulation factors, which are traditionally regarded as components of the haemostatic system involved in the arrest of bleeding, are also contributors to other common diseases such as cancer [6, 7].

The aim of this chapter is to review the association of COPD with thrombotic disorders in terms of epidemiology, clinical and laboratory features, in order to understand the processes that are in play and, therefore, have a possible bearing on the management of this important condition. Studies in this area are not easy to conduct because of the separate, but overlapping, impacts of smoking, disease progression and acute exacerbations, all of which can make elucidation of cause and effect difficult to assess. However, COPD, along with other conditions that are associated with

local and systemic inflammation and which undergo periodic exacerbations, such as inflammatory bowel disease [8], provides an attractive model for studying the links between inflammation, infection, development of a prothrombotic state and cardiovascular diseases (CVD).

Epidemiology

The association of COPD with CVD was analysed in a recent UK General Practice Research Database (GPRD)-based study in primary care [9]. Using a case-control design, 35,772 patients with COPD were compared with the same number of age- and sex-matched controls. Current or former smoking and prevalent cardiovascular disease (acute myocardial infarction (MI) or ischaemic heart disease (IHD), congestive heart failure (CHF), stroke or transient ischaemic attack (TIA), DVT and PE) were more common in those with COPD. Cases and controls, free of cardiovascular disease, were followed up for incident events. Incidence rates of MI, stroke/TIA, DVT and PE were all higher in COPD patients. After adjustment for possible confounding factors, including smoking, incident MI and PE remained higher in patients with COPD with odds ratios (95% confidence interval) of 1.40 (1.13–1.73) and 2.51 (1.62–3.87), respectively. In those with severe COPD on the grounds that oxygen treatment was required, the risk of MI was increased three-fold (3.00 (1.53–5.86)) and that of PE was increased over seven-fold (7.47 (2.35–23.7)). Risks of a similar order have been observed in other studies [10, 11].

Associations have also been observed between acute exacerbations of COPD and a short-term increased risk of both MI and stroke. Using a primary care database in England and Wales that included 25,857 patients with COPD, it was reported that there was an increased risk of an MI in the 5 days following exacerbations of COPD (2.27 (1.1–4.7)) as well as a smaller increase in the risk of a stroke [12]. This is consistent with evidence of a short-term increase in the risk of arterial and venous thrombosis following respiratory tract infections in the general population [13–15].

A further retrospective analysis of data from the National Hospital Discharge Survey compared the rates of diagnosis of PE and DVT in 58,392,000 adults hospitalised with COPD with those of 799,403,000 adults hospitalised for other reasons [16]. Compared to subjects without COPD, the relative risk (RR) of PE for those hospitalised with COPD was 1.92. For DVT the equivalent RR was 1.30. Again this supports COPD as a risk factor for VTE, this time in hospitalised patients, and also suggests that COPD may be more strongly associated with PE than with DVT.

Increased recognition of the importance of PE in COPD has come about in part through the advent of computed tomography (CT) scanning, which allows the more accurate detection of PE in COPD patients. Thus one single-centre study of 197 patients who underwent spiral CT angiography following admission to hospital with an unexplained severe exacerbation of COPD reported that PE were present in 25% of such patients [17]. A subsequent systematic review and meta-analysis came to a similar conclusion for patients with a sufficiently severe exacerbation as to require admission to hospital [18]. Interestingly, although DVT and PE are regarded as the same condition with the latter arising from the former, once more the prevalence of PE appears to be higher than for DVT in the same population of COPD patients. It has been suggested, on the basis of trans-oesophageal echocardiographic appearances, that some apparent pulmonary emboli might arise as a result of *in situ* thrombosis rather than embolism [18].

PE also appears to be an important cause of death in patients with COPD. A recent autopsy study of 43 patients, who had died following admission with an exacerbation of COPD, found that PE was the third most common cause of death (21%) after cardiac failure (37%) and pneumonia (28%) [19]. This finding is consistent with previous reports. Moreover, the case-fatality rate from PE in patients with COPD may be higher than in patients without COPD. In the Computerized Registry of Patients with Venous Thromboembolism (RIETE) registry of patients presenting with symptomatic, objectively confirmed VTE, a total of 2,984 patients with COPD (10%) were compared with 25,936 patients without COPD [20]. Mortality at 7 and 90 days was significantly higher in patients with COPD and the major single cause of death at both time-points was PE

(52 out of 78 deaths by day seven and 69 out of 320 deaths by day 90). As well as the initial VTE event in patients with COPD being more often a PE (in contrast to patients without COPD), recurrent events by 90 days were also more likely to be PE. Minor, but not major, bleeding on anticoagulant therapy was more common in patients with COPD than those without.

Overall, while a direct causal relationship cannot be inferred, there appears to be a strong association of COPD with a clinical manifestation of both arterial thromboembolism and VTE that are independent of smoking. The associations, which are significant in the basal state, become even more pronounced following acute exacerbations and may contribute substantially to the morbidity and mortality associated with this condition.

Pathogenesis of thrombosis

Virchow's triad of vessel wall disturbance, thrombogenicity of the blood and stasis of blood flow remains pertinent to the understanding of thrombosis.

Vessel wall disturbance is macroscopically visible in arterial disease with atheroma. Significant advances have been made in understanding the pathogenesis of this condition. Whilst atheroma formation is clearly multifactorial, components of the haemostatic system are thought to play an important role in its progression, as recently comprehensively reviewed [21]. Although VTE has been regarded separately from arterial disease in terms of aetiology and pathogenesis, there is increasing recognition of an important overlap between the two conditions in terms of occurrence and risk factors [22–25]. Endothelial disturbance is important in the pathogenesis of VTE as well as IHD [24].

Thrombogenicity is important in the development of both venous and arterial thrombosis [1, 21, 25, 26]. Acute coronary syndromes classically arise as a result of the rupture of an unstable plaque within the arterial wall, thereby exposing tissue factor-rich contents to blood containing factor VII. A coordinated sequence of reactions on phospholipid surfaces as provided by activated platelets, for example, then follows leading to the generation of thrombin, a key serine protease that converts soluble fibrinogen into an insoluble fibrin clot, activates platelets through binding to specific receptors (protease-activated receptor (PAR)-1 and PAR-4), and participates in a positive feedback loop to increase its own generation. Platelets adhere, through specific receptors, to collagen and immobilised von Willebrand factor (vWF) found in the wall of the damaged vessels. They then undergo a process of activation, which involves the release of their contents, leading to further platelet activation and expression of integrin receptors on their surfaces resulting in platelet aggregation through binding of adjacent platelets *via* fibrinogen and vWF. Although platelets and the proteins of the coagulation system have traditionally been studied separately, it is clear that their functions are highly integrated biologically in both haemostasis and thrombosis.

Clearly reduced blood flow is also important in thrombus formation, be it the result of local reduction adjacent to the wall of a coronary artery affected by atheroma, or within the lower limbs as a result of immobility and thereby predisposing to DVT.

Association between haemostatic and inflammatory systems

Historically these systems have been studied separately, because of the obvious clinical importance of platelets and clotting factors in the arrest of bleeding, for which the key properties are the rapid and localised response to vessel wall injury. In contrast, predisposition to thrombosis is less visible and takes place over a longer timeframe. It has become increasingly evident that haemostasis and inflammation are closely linked at any number of levels. Examples are shown in table 1.

Markers of haemostatic activation in COPD

A number of studies have measured levels of variables associated with haemostasis and thrombosis. Inevitably the studies are difficult to compare and are complicated by confounding impacts of

Table 1. Examples of links between haemostatic and inflammatory systems

IL-6 induces tissue factor expression on mononuclear cells [3]
Thrombin and factor Xa enhance production of IL-1 [3]
Tissue factor-FVIIa binding to PAR-2 upregulates inflammatory responses in macrophages [3]
TNF- α and IL-1 β downregulate endothelial expression of thrombomodulin [3]
Fibrinogen is an acute phase reactant that increases production of TNF- α and IL-8 [4, 27]
IL-8, IL-6 and TNF- α increase release of ultra-large vWF multimers from endothelium [4]
Thrombin amplifies activation of complement [28]
Activated platelets amplify activation of complement [28]
Complement upregulates tissue factor expression on leukocytes and endothelial cells [28]
Complement induces shedding of heparan sulfate from endothelial cells [28]

IL: interleukin; PAR: protease-activated receptor; TNF- α : tumour necrosis factor- α ; vWF: von Willebrand factor.

smoking, disease severity, current or recent exacerbations and possible effects of treatments, such as steroids. However, they are important in shedding light on the possible mechanisms that might link COPD with its cardiovascular complications. Focus here is given to variables within the haemostatic system recognising the overlap with systemic inflammatory variables that have been extensively studied. A simplified outline of the coagulation system is shown in figure 1.

Tissue factor

Tissue factor (TF) is a transmembrane glycoprotein that binds activated factor VII (FVIIa) which then initiates coagulation. TF is not normally present on the inner endothelial lining of blood vessels but is constitutively expressed on the surrounding cells, such as vascular smooth muscle cells and adventitial fibroblasts [21]. Whether functional TF is present in circulating blood is controversial [1]. If so, the quantities must be extremely small or widespread thrombosis would occur [30]. If present in blood, its potential source is uncertain. Experimentally, its expression on endothelial cells can be upregulated by inflammatory signals, whether this happens *in vivo* is unclear. It may arise from monocytes activated by pro-inflammatory cytokines including those present in microparticles. Elevated levels of active TF have been described, for example, in patients with acute ischaemic stroke and acute coronary disease [30, 31]. In one study, circulating TF activity was found to be significantly increased in all 11 patients with stable, but severe, COPD in whom it was analysed [32]. A further recent study reported measurable quantities of TF in 12% of 60 COPD patients with stable disease and these patients tended to have evidence of higher levels of inflammatory markers (C-reactive protein (CRP), interleukin (IL)-6 and fibrinogen) and thrombin generation [33].

Factor XI

Factor XI (FXI) is activated (FXIa) by activated FXII (FXIIa), thrombin and polyphosphate derived from activated platelets [1, 30]. Unlike FXII, FXI is necessary for normal haemostasis and it both activates coagulation *via* FIX and impairs fibrinolysis through activation of thrombin-activatable fibrinolysis inhibitor (TAFI). Emerging evidence suggests that both FXIa and FXIIa may be involved in the pathogenesis of arterial thrombosis [1, 21, 30, 33, 34]. Elevated levels of FXIa were reported in 13% of 60 patients with stable COPD and, as with TF, were associated with higher levels of inflammatory markers and thrombin generation [33].

Thrombin generation

In a recent study of 60 patients with COPD, a number of coagulation and naturally occurring anticoagulants were measured and used to estimate thrombin generation computationally [35]. Compared with 43 age-, sex- and smoking status-matched healthy controls, patients with COPD had increased rates and amounts of thrombin generation. This appeared to be mainly driven by increased levels of FVIII clotting activity (FVIIIc), FIXc, prothrombin and reduced free tissue

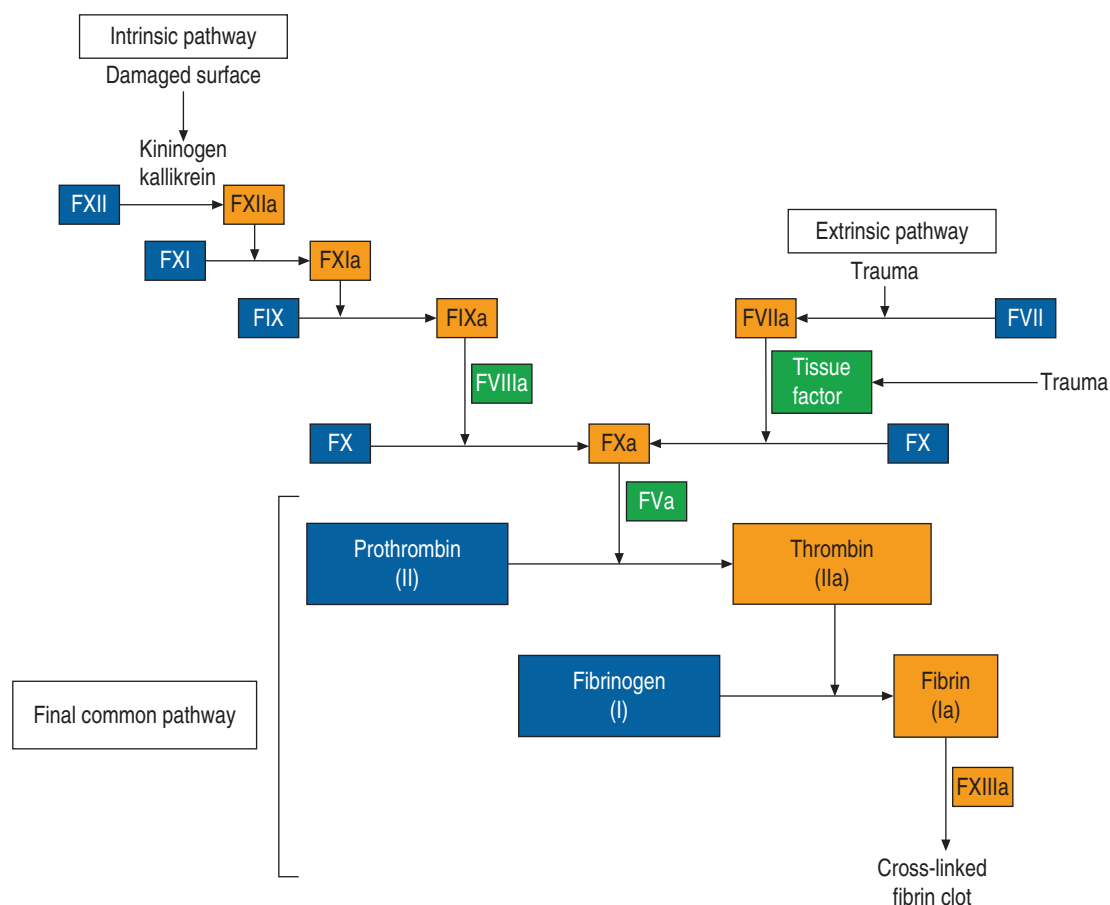


Figure 1. Outline of plasma coagulation system. F: factor; a: activated factor. Reproduced and modified from [29] with permission from the publisher.

factor pathway inhibitor (TFPI), an inhibitor of coagulation. In a case-control study in 60 patients with stable COPD, thrombin-antithrombin (TAT) complexes were significantly higher than in the controls, indicating increased thrombin generation [32].

In a study of 20 stable patients with mild COPD, a 2-hour hypoxic challenge was associated with evidence of increased thrombin generation and of inflammation [36]. Levels of prothrombin fragment F1+2 and TAT complex (both markers of thrombin generation) rose significantly, as did IL-6, whereas these changes were not seen in those who remained breathing air.

In a study that looked at 30 patients 24-48 hour after hospital admission with an exacerbation of COPD, levels of F1+2 were significantly elevated when compared with levels measured when the patients were clinically stable 4 weeks later [37].

Fibrinogen

Elevated fibrinogen levels are associated with a risk of cardiovascular disease [38]. Fibrinogen contributes to a thrombotic predisposition through a number of mechanisms including plasma viscosity, platelet aggregation, increased fibrin formation, binding of leukocytes to endothelial cells, and promotion of inflammatory responses [27, 39]. As an acute-phase protein, it is not surprising that levels are significantly elevated in patients with COPD and become further elevated during acute exacerbations. Thus, the East London COPD study followed 93 COPD patients for 1 year with daily diary cards [40]. During this period, 67 patients were admitted with 120

exacerbations. Their mean baseline fibrinogen concentration was $3.9 \text{ g}\cdot\text{L}^{-1}$, higher than that of an age-matched healthy population of $3.1 \text{ g}\cdot\text{L}^{-1}$. Exacerbations were associated with significant increases in both fibrinogen and IL-6, but levels had reverted to baseline levels by 6 weeks. Greater rises in fibrinogen were associated with higher baseline levels, increasing age, purulent sputum and the presence of upper respiratory tract symptoms. In a subsequent study, baseline fibrinogen was higher in carriers of respiratory syncytial virus and the rise in fibrinogen was higher in viral exacerbations than non-viral exacerbations [41]. These data suggest that virus-induced exacerbations may stimulate an acute phase response and thereby contribute to links between COPD and IHD.

Fibrin

Fibrin is the end consequence of activating the coagulation system, formed through the action of thrombin upon fibrinogen. It is, therefore, the key component of both arterial and venous thrombi and also contributes to the progression of atheromatous plaques. Fibrin consists of a network of cross-linked fibres with variable resistance to lysis. The latter is partly determined by the structure of the fibrin clot in terms of fibre thickness and pore size. In a study of 56 patients with stable COPD, lower clot permeability rates and denser clot structures were reported in when compared with age- and sex-matched control subjects [42]. These findings were associated with increases in CRP levels. The COPD patients in this study were randomly assigned to take or not take a daily dose of simvastatin (40 mg) for 3 months. Interestingly, it was found that the clots became more permeable, less compact and more easily lysed following statin therapy.

D-dimer

D-dimer is a marker of fibrin turnover. Elevated levels are associated with an increased risk of IHD in healthy populations and are widely used in diagnostic algorithms for VTE [43–45]. D-dimer levels are also elevated in a variety of inflammatory conditions, *e.g.* during pregnancy and in cancer. In a study of 30 patients with COPD, D-dimer was increased at presentation with an acute exacerbation and had decreased when re-measured approximately 4 weeks later [37].

Von Willebrand factor and factor VIII

vWF serves two main functions in the haemostatic system: it binds to the glycoprotein (GP)-Ib/V/IX and IIb/IIIa receptors on platelets, thereby promoting the processes of platelet adhesion and aggregation, and it is the carrier for FVIII, an essential component of the coagulation system [46]. It is synthesised by endothelial cells and elevated levels are often viewed as a marker of endothelial perturbation. Both vWF and FVIIIc behave as acute phase reactants. Elevated levels of vWF and/or FVIIIc are associated with increased risks of IHD and VTE [47, 48]. In COPD, FVIII activity was reported to be significantly elevated in 60 patients with stable COPD compared with 43 healthy controls [35]. vWF was elevated in 30 patients at the time of a COPD exacerbation and had reduced significantly on follow-up approximately 4 weeks later [37].

Naturally occurring anticoagulants

These protein molecules serve to regulate thrombin generation and activity and include antithrombin, protein C, protein S and TFPI. Low levels are associated with increased risk of VTE. In a study of 60 patients with stable COPD, antithrombin and protein C activities were similar to the levels found in the control subjects; however, free TFPI levels were significantly reduced [35]. Other studies have not found TFPI to be reduced, but have used different methodologies. Since thrombin generation is increased in COPD, this lack of increase in naturally occurring anticoagulants suggests a failure to compensate, which is consistent with a prothrombotic tendency.

Platelet activation in COPD

The optimal methods for estimating platelet activation remain the subject of debate. One marker, which is elevated in acute coronary syndromes and in smokers, is the presence of circulating platelet–monocyte aggregates detected by flow cytometry. Activated platelets release cytokines and chemokines and express CD40L on their surface, leading to monocyte binding and the formation of detectable platelet–monocyte aggregates. One recent study involving 18 COPD patients and 16 age-matched controls, all of whom were ex-smokers, reported that platelet–monocyte aggregates were increased in the patient group [49]. Moreover, platelet–monocyte aggregates were increased in a separate group of 12 patients during an acute exacerbation when compared with the levels at follow-up, at least 2 weeks later. This study also reported higher numbers of circulating monocytes and platelets in COPD patients, although still within the normal range, suggesting that both greater activation and increased numbers of platelets might contribute to CVD risk in patients with COPD [49].

Summary of changes in stable COPD and at exacerbation

In summary, the observations reported previously suggest that stable COPD is associated with significant increases in platelet activation, thrombin generation, fibrinogen concentration and fibrin turnover, without a compensatory increase in naturally-occurring anticoagulants. The precise mechanisms of these alterations have not yet been defined, but it seems likely that pulmonary and systemic inflammation, which characterise COPD, are responsible. These haemostatic system responses may reciprocally activate the inflammatory system and provide a link between the latter and the development of thrombosis. The changes that are observed in the stable state appear to be more pronounced during acute exacerbations and, together with impaired mobility, may contribute to the cardiovascular outcomes that are further increased at such time.

Venous thromboembolism and COPD: clinical issues

Prevention

Until recently VTE was an under-appreciated complication of COPD, probably reflecting the clinical similarity between PE and COPD exacerbations. However, as discussed earlier, observational data showing COPD to be a risk factor for VTE in hospitalised patients [16], together with evidence suggesting the mortality from PE is higher in patients with COPD [20], makes it imperative that thromboprophylaxis is considered in patients with COPD who are admitted to hospital. A number of trials of pharmacological thromboprophylaxis in hospitalised medical patients have shown reductions in VTE risk when compared with placebo, and subgroup analyses have reported similar benefits in those with respiratory diseases. In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, in which enoxaparin 40 mg·day⁻¹ was compared to placebo in 1,102 acutely ill medical patients (over 50% of whom had severe respiratory disease) [50], a *post hoc* analysis in those with chronic respiratory failure showed that enoxaparin reduced the risk of VTE by 74% (OR 0.26 (95% CI 0.10–0.68), *p*=0.005) [51]. In the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT), in which a daily dose of dalteparin (5,000 IU) was compared to placebo, the rate of VTE or sudden death by day 21 in patients with acute respiratory failure was 3% with dalteparin and 5% in those taking the placebo (OR 0.72 (95% CI 0.38–1.34)) [52]. In a trial of fondaparinux for VTE prevention in medical inpatients, four (5.5%) out of 73 patients with acute respiratory illness developed VTE taking the placebo compared to one (1.6%) out of 63 patients taking the fondaparinux [53]. Finally in a study of 223 patients with acute decompensated COPD on mechanical ventilation, thromboprophylaxis with the low molecular-weight heparin (LMWH), nadroparin, significantly reduced the incidence of VTE compared with placebo from 28.2% to 15.5% in 169 evaluable patients, although the majority of episodes were distal DVT [54]. In the

current national VTE risk-assessment tool, for use in adults admitted to hospital in England, medical comorbidity including respiratory pathology is included as a risk factor for thrombosis and such individuals should be considered for pharmacological prophylaxis in the absence of a contraindication. This is consistent with other guidelines [55].

Management

Most fatal PEs arose because of a failure of diagnosis rather than a failure of treatment. Given the high prevalence of PE in patients admitted with COPD exacerbations, it is, therefore, incumbent upon clinicians to have a high index of suspicion in such patients so that treatment is not delayed until it is too late. The increased risk of recurrence as PE and the higher mortality compared to non-COPD patients [20] has a potential bearing on recommendations for duration of anticoagulant therapy in patients with COPD. Guidelines recommend that an extended course of anticoagulant therapy be considered in patients with unprovoked PE because of the risks of recurrence [56]. Given the higher incidence of recurrent PE and the increased PE-related mortality in COPD, there is a case for considering extended anticoagulation for prevention of recurrent PE in all patients with COPD, unless there was an additional transient-provoking risk factor no longer present or an anticoagulant-related problem (e.g. bleeding) arose. Recent clinical trials of new (non-vitamin-K based) oral anticoagulants, such as rivaroxaban (an inhibitor of activated FX) [57] and dabigatran (an inhibitor of thrombin) [58], in the treatment of VTE may alter the balance of risks and benefits in long-term secondary prevention of VTE in patients with COPD, as well as in other populations, particularly as they are less affected by interactions with antibiotics and other medications than warfarin.

Diagnosis

The optimal approach to the diagnosis of suspected PE in patients with COPD has not been comprehensively evaluated. In one study of 3,306 patients with suspected PE (82% of whom were outpatients), a standard approach using a clinical decision rule (Wells score) and D-dimer excluded PE in 23% of 341 patients with COPD compared to 32% in the total study population with a 1.3% (95% CI 0.03–7.0%) incidence of VTE in the 3 months of follow-up, similar to that of the cohort as a whole but with a wider confidence interval [59].

CT pulmonary angiography (CTPA) remains the standard imaging approach to the diagnosis of PE in patients with COPD. Its diagnostic accuracy in patients with suspected PE appears to be similar in patients with or without COPD [60]. It has the additional advantage of enabling diagnosis of alternative conditions that clinically mimic PE. In contrast, planar ventilation/perfusion (V'/Q') scintigraphy in patients with COPD has been less satisfactory, because of the high proportion of intermediate probability or non-diagnostic scans [60]. The advent of tomographic V'/Q' scans (V'/Q' SPECT)) appears to be an advance for patients with COPD with higher sensitivity and specificity [61] and, therefore, may be particularly useful in patients with renal impairment or contrast allergy in which CTPA is contraindicated. In such patients, Technegas is preferred over liquid aerosols, although in rare patients with emphysema Technegas particles may be trapped in bullae causing a pattern that may be mistaken for a mismatch [61].

Summary of evidence of association of COPD and VTE

There is evidence of an important association between COPD and risk of VTE, particularly when patients are admitted to hospital because of acute exacerbations. The reasons are probably multifactorial and include prothrombotic changes and reduced mobility. The association seems stronger for PE than for DVT, for reasons that have yet been defined. PE is a leading cause of death in COPD patients. It is, therefore, important that such patients are considered for thromboprophylaxis at the time of hospital admission. About 25% of patients with COPD admitted to hospital with an unexplained exacerbation have evidence of underlying PE. The clinical features are similar to those of other exacerbations and, therefore, a high index of suspicion is needed. The advent of CTPA has facilitated the diagnosis of PE in patients with COPD.

Conclusion

There is increasing evidence that COPD should be regarded as an important risk factor for thrombotic manifestations of both venous and arterial disease. Epidemiological evidence is consistent with this view and plausible underlying mechanisms have been identified. Although clinical trials of cardiovascular prevention have not been undertaken expressly in patients with COPD, the cumulative data suggest that pharmacological intervention should be widely offered to patients with COPD, in addition with advice to stop smoking. Risks of VTE should also be considered, particularly following admission to hospital. When VTE is diagnosed in patients with COPD, consideration should be given to extended secondary prophylaxis after the initial 3 months of treatment. There is an overlap between risk factors for arterial disease and VTE, so adoption of healthy lifestyle factors should be encouraged in all patients with COPD.

Statement of Interest

None declared.

References

1. Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med* 2008; 359: 938–949.
2. Mathers CD, Boerma T, Ma Fat D. Global and regional causes of death. *Br Med Bull* 2009; 92: 7–32.
3. Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. *Circulation* 2004; 109: 2698–2704.
4. Esmon CT. The interactions between inflammation and coagulation. *Br J Haematol* 2005; 131: 417–430.
5. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685–1695.
6. Jain S, Harris J, Ware J. Platelets: linking hemostasis and cancer. *Arterioscler Thromb Vasc Biol* 2010; 30: 2362–2367.
7. Nierodzik ML, Karparkin S. Thrombin induces tumor growth, metastasis, and angiogenesis: evidence for a thrombin-regulated dormant tumor phenotype. *Cancer Cell* 2006; 10: 355–362.
8. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010; 375: 657–663.
9. Schneider C, Bothner U, Jick SS, *et al.* Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. *Eur J Epidemiol* 2010; 25: 253–260.
10. Sidney S, Sorel M, Quesenberry CP Jr, *et al.* COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005; 128: 2068–2075.
11. Curkendall SM, deLuise C, Jones JK, *et al.* Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada. Cardiovascular disease in COPD patients. *Ann Epidemiol* 2006; 16: 63–70.
12. Donaldson GC, Hurst JR, Smith CJ, *et al.* Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.
13. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis* 2009; 9: 601–610.
14. Dong M, Liu T, Li G. Association between acute infections and risk of acute coronary syndrome: a meta-analysis. *Int J Cardiol* 2011; 147: 479–482.
15. Clayton TC, Gaskin M, Meade TW. Recent respiratory infection and risk of venous thromboembolism: case-control study through a general practice database. *Int J Epidemiol* 2011; 40: 819–827.
16. Stein PD, Beemath A, Meyers FA, *et al.* Pulmonary embolism and deep venous thrombosis in hospitalized adults with chronic obstructive pulmonary disease. *J Cardiovasc Med (Hagerstown)* 2007; 8: 253–257.
17. Tillie-Leblond I, Marquette CH, Perez T, *et al.* Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006; 144: 390–396.
18. Rizkallah J, Man SFP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD. A systematic review and metaanalysis. *Chest* 2009; 135: 786–793.
19. Zvezdin B, Milutinov S, Kojic M, *et al.* A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. *Chest* 2009; 136: 376–380.
20. Bertolotti L, Quenet S, Mismetti P, *et al.* Clinical presentation and outcome of venous thromboembolism in COPD. *Eur Respir J* 2012; 39: 862–868.
21. Borisssoff JJ, Spronk HMH, ten Cate H. The hemostatic system as a modulator of atherosclerosis. *N Engl J Med* 2011; 364: 1746–1760.
22. Prandoni P, Bilora F, Marchiori A, *et al.* An association between atherosclerosis and venous thrombosis. *N Eng J Med* 2003; 348: 1435–1441.
23. Goldhaber SZ. Risk factors for venous thromboembolism. *J Am Coll Cardiol* 2010; 56: 1–7.

24. Piazza G, Goldhaber SZ. Venous thromboembolism and atherosclerosis: an integrated approach. *Circulation* 2010; 121: 2146–2150.
25. Lowe GDO. Common risk factors for both arterial and venous thrombosis. *Br J Haematol* 2008; 140: 488–495.
26. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007; 357: 2482–2494.
27. Hodgkinson CP, Patel K, Ye S. Functional toll-like receptor 4 mutations modulate the response to fibrinogen. *Thromb Haemost* 2008; 100: 301–307.
28. Markiewski MM, Nilsson B, Ekdahl KN, *et al.* Complement and coagulation: strangers or partners in crime? *Trends Immunol* 2007; 28: 184–192.
29. AnaesthesiaUK. Coagulation classical model. www.frca.co.uk/article.aspx?articleid=100096. Date created August 20, 2005. Date last accessed December 28, 2012.
30. Undas A, Slowik A, Gissel M, *et al.* Active tissue factor and activated factor XI in patients with acute ischemic cerebrovascular events. *Eur J Clin Invest* 2012; 42: 123–129.
31. Butenas S, Undas A, Gissel MT, *et al.* Factor XIa and tissue factor activity in patients with coronary artery disease. *Thromb Haemost* 2008; 99: 142–149.
32. Vaidula VR, Criner GJ, Grabianowski C, *et al.* Circulating tissue factor procoagulant activity is elevated in stable moderate to severe chronic obstructive pulmonary disease. *Thromb Res* 2009; 124: 259–261.
33. Jankowski M, Undas A, Kaczmarek P, *et al.* Activated factor XI and tissue factor in chronic obstructive pulmonary disease: links with inflammation and thrombin generation. *Thromb Res* 2011; 127: 242–246.
34. Gailani D, Renné T. Intrinsic pathway of coagulation and arterial thrombosis. *Arterioscler Thromb Vasc Biol* 2007; 27: 2507–2513.
35. Undas A, Jankowski M, Kaczmarek P, *et al.* Thrombin generation in chronic obstructive pulmonary disease: dependence on plasma factor composition. *Thromb Res* 2011; 128: e24–e28.
36. Sabit R, Thomas P, Shale DJ, *et al.* The effects of hypoxia on markers of coagulation and systemic inflammation in patients with COPD. *Chest* 2010; 138: 47–51.
37. Polosa R, Malerba M, Cacciola RR, *et al.* Effect of acute exacerbations on circulating endothelial, clotting and fibrinolytic markers in COPD patients. *Intern Emerg Med* [Epub ahead of print DOI: 10.1007/s11739-011-0636-1].
38. Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 2005; 294: 1799–1809.
39. Davalos D, Akassoglou K. Fibrinogen as a key regulator of inflammation in disease. *Semin Immunopathol* 2012; 34: 43–62.
40. Wedzicha JA, Seemungal TAR, MacCallum PK, *et al.* Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000; 84: 210–215.
41. Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
42. Undas A, Kaczmarek P, Sladek K, *et al.* Fibrin clot properties are altered in patients with chronic obstructive pulmonary disease. Beneficial effects of statin treatment. *Thromb Haemost* 2009; 102: 1176–1182.
43. Danesh J, Whincup P, Walker M, *et al.* Fibrin D-dimer and coronary heart disease: prospective study and meta-analysis. *Circulation* 2001; 103: 2323–2327.
44. Righini M, Perrier A, De Moerloose P, *et al.* D-dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost* 2008; 6: 1059–1071.
45. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012; 379: 1835–1846.
46. Mannucci PM. Treatment of von Willebrand's disease. *N Engl J Med* 2004; 351: 683–694.
47. Danesh J, Wheeler JG, Hirshfield GM, *et al.* C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; 350: 1387–1397.
48. Jenkins PV, Rawley O, Smith OP, *et al.* Elevated factor VIII levels and risk of venous thrombosis. *Br J Haematol* 2012; 157: 665–63.
49. Maclay JD, McAllister DA, Johnston S, *et al.* Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax* 2011; 66: 769–774.
50. Samama MM, Cohen AT, Darmon JY, *et al.* A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999; 341: 793–800.
51. Alikhan R, Cohen AT, Combe S, *et al.* Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. *Blood Coagul Fibrinolys* 2003; 14: 341–346.
52. Cohen AT, Turpie AG, Leizorovicz A, *et al.* Thromboprophylaxis with dalteparin in medical patients: which patients benefit? *Vasc Med* 2007; 12: 123–127.
53. Cohen AT, Davidson BL, Gallus AS, *et al.* Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 2006; 332: 325–329.
54. Fraisse F, Holzapfel L, Coulaud J-M, *et al.* Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. *Am J Respir Crit Care Med* 2000; 161: 1109–1114.
55. Kahn SR, Lim W, Dumm AS, *et al.* Prevention of VTE in nonsurgical patients. antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: 195S–226S.

56. Kearon C, Akl EA, Comerota AJ, *et al.* Antithrombotic therapy for VTE disease. antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: 419S–494S.
57. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499–2510.
58. Schulman S, Kearon C, Kakkar AK, *et al.* Dabigatran *versus* warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; 361: 2342–2352.
59. Sohne M, Kruip MJHA, Nijkeuter M, *et al.* Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure and in older patients with suspected pulmonary embolism. *J Thromb Haemost* 2006; 4: 1042–1046.
60. Hartmann IJC, Hagen PJ, Melissant CF, *et al.* Diagnosing acute pulmonary embolism: effect of chronic obstructive pulmonary disease on the performance of D-dimer testing, ventilation/perfusion scintigraphy, spiral computed tomographic angiography, and conventional angiology. *Am J Respir Crit Care Med* 2000; 162: 2232–2237.
61. Bajc M, Neilly JB, Miniati M, *et al.* EANM guidelines for ventilation/perfusion scintigraphy. *Eur J Nucl Med Mol Imaging* 2009; 36: 1356–1370.

Chapter 16

Comorbidities in current COPD guidelines



Per Sigvald Bakke^{*,#}

SUMMARY: Altogether, nine international guidelines on the management of COPD published between 2004 and 2012 were reviewed for their focus on comorbidities. The guidelines differed greatly in their coverage of comorbidities. This related to the number of times the topic was mentioned, in what aspects of COPD management comorbidity were addressed, what type of comorbidities were considered and, finally, what was actually stated about the various comorbidities. There was no time trend in the quantitative and qualitative content of comorbidities in the guidelines. The guideline with the highest coverage of comorbidities was that of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The increasing knowledge of the significance of comorbidities in COPD is likely to be reflected in an enhanced focus on this aspect in future COPD guidelines.

KEYWORDS: COPD, comorbidities, guidelines

^{*}Institute of Medicine, University of Bergen, and
[#]Dept of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway.

Correspondence: P.S. Bakke, Institute of Medicine, University of Bergen, Postbox 7804, N-5020 Bergen, Norway.
Email: per.bakke@med.uib.no

Eur Respir Monogr 2013; 59: 217–222.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10012612
Print ISBN: 978-1-84984-032-3
Online ISBN: 978-1-84984-033-0
Print ISSN: 1025-448x
Online ISSN: 2075-6674

COPD often coexists with other diseases, referred to as comorbidities of COPD. The comorbidities may share common risk factors with COPD, or represent extrapulmonary manifestations of COPD or complications of the disease [1, 2].

Comorbidities contribute to the overall severity and manifestation of the disease. They have a major impact on quality of life and survival [2]. As such, comorbidities of COPD are important to assess along with diagnoses and differential diagnosis, treatment, follow-up and prognosis of COPD, as well as with handling of exacerbations of COPD. All these aspects of COPD are important parts of guidelines of COPD management. However, limited data are available as to what extent the guidelines address comorbidities when describing the various aspects of the COPD management.

Methods

The search for COPD guidelines was performed in two ways. First, the web pages of the dominant international lung societies were searched for guidelines of COPD: the American Thoracic Society (ATS), American College of Chest Physicians (ACCP), Asian and Pacific Society of Respiriology (APSR), European Respiratory Society (ERS), and International Union Against Tuberculosis and Lung Disease (IUATLD). Secondly, PubMed was searched using the terms “Guidelines AND COPD”. The search was restricted to manuscripts in the English language, published after 2000. From these hits, papers discussing the guidelines were excluded, as were COPD guidelines not

addressing management of the disease. For example, an ERS paper on guidelines for epidemiological studies on COPD and an ATS/ERS paper on recommendations for outcomes in COPD pharmacological trials were excluded [3, 4].

This strategy for finding guidelines on COPD management provided nine documents, listed in table 1 [5–13]. In some cases, several versions of the original guidelines were available; the latest version of these guidelines was used.

The guidelines were then screened for the term “comorbidities”. The comorbidities that were mentioned were recorded as were the parts of the guidelines in which the comorbidities were addressed, *i.e.* diagnosis, treatment or prognosis of COPD. Finally, a qualitative assessment was performed to assess whether a comorbidity was only mentioned by name or whether the rationale for and the consequences of mentioning a specific comorbidity were also given.

Results

The guidelines selected were published between 2004 and 2012 (table 1). Some of the societies, like ATS and ERS, have several guidelines that partly overlap, such as guidelines 1, 2 and 7 (table 1). Several authors have contributed to various guidelines in table 1. Some of the guidelines are restricted to parts of COPD management, such as rehabilitation (guideline 2) and noninvasive ventilation (guideline 3), while others include the whole picture of COPD management (guidelines 1, 6 and 8).

All of the guidelines addressed the term “comorbidity”, with the exception of the guideline on the diagnosis and management of stable COPD from 2007 (guideline 4) and the guideline on noninvasive ventilation of type 2 respiratory failure in COPD from 2008 (guideline 5) (table 2). The 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline (guideline 8) mentioned the term comorbidity 71 times; the other guideline referring frequently to comorbidities

Table 1. The guidelines included in the current review by issuing society and year of publication			
Guideline number	Society	Year of publication	Title of guideline [ref.]
1	ATS and ERS	2004	Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper [5]
2	ATS and ERS	2006	American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation [6]
3	BTS	2007	Intermediate care – hospital-at-home in chronic obstructive pulmonary disease: British Thoracic Society guideline [7]
4	ACP	2007	Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians [8]
5	RCP and BTS	2008	Non-invasive ventilation in chronic obstructive pulmonary disease: management of acute type 2 respiratory failure [9]
6	RCP	2010	Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care [10]
7	ACP, ACCP, ATS and ERS	2011	Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society [11]
8	GOLD	2011	Global strategy for the diagnosis, management, and prevention of COPD (revised 2011) [12]
9	ATS	2012	An official American Thoracic Society workshop report: the integrated care of the COPD patient [13]

ATS: American Thoracic Society; ERS: European Respiratory Society; BTS: British Thoracic Society; ACP: American College of Physicians; RCP: Royal College of Physicians; ACCP: American College of Chest Physicians; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

was the 2004 ERS/ATS guideline (guideline 1). There was no trend among the other guidelines suggesting that more recent guidelines addressed the topic more frequently than the older ones (table 2).

The GOLD guideline (guideline 8) was one of two with a specific section addressing comorbidities of COPD. The section covered both management of comorbidities in patients with COPD and management of COPD in patients with comorbidities. The comorbidities addressed included cardiovascular disease, diabetes mellitus, osteoporosis, anxiety and depression, lung cancer, infections, and metabolic syndrome. In addition, comorbidities were mentioned in sections covering assessment and diagnosis of the disease, therapeutic options, management of stable COPD, and management of exacerbations. It is worth noting that there was no consistency as to what comorbidities were addressed in the various sections of the GOLD guideline. For instance, muscle dysfunction was mentioned only in the assessment section.

The other guideline with a specific section on comorbidity was the 2006 ATS/ERS guideline on pulmonary rehabilitation (guideline 2) in which anxiety and depression were of particular focus. The 2004 ATS/ERS guideline (guideline 1) focuses on comorbidities when addressing assessment, treatment, prognosis and management of the disease. The specific comorbidities mentioned are heart disease, renal and liver failure, diabetes mellitus and depression.

In the other guidelines addressing comorbidities, those mentioned most frequently are heart disease, depression, anxiety and osteoporosis. With the exception of the GOLD guideline (guideline 8), none of the guidelines mention lung cancer, metabolic syndrome or gastro-oesophageal reflux.

Table 2. Guidelines included in this review according to information on comorbidity					
Guideline number [#]	The term “comorbidity”		Chapter on comorbidities	Comorbidities mentioned in text	Part of text addressing comorbidities
	Times mentioned	Mentioned in summary			
1	19	N/A	No	Heart disease, renal and liver failure, diabetes, depression	Diagnosis, management
2	6	N/A	Yes [†]	Peripheral muscle, cardiac, nutritional and psychosocial dysfunction	Diagnosis, management, prognosis
3	3	Yes	No	Heart disease	Diagnosis
4	0	No	No	None	
5	0	No	No	None	
6	6	N/A	No	Anxiety, depression, heart failure, osteoporosis, diabetes	Management
7	1	No	No	None	
8	71	Yes	Yes ⁺	Heart disease, diabetes, anxiety, depression, lung cancer, infections, metabolic syndrome, osteoporosis, muscle dysfunction, anorexia	Diagnosis, management, prognosis
9	8	No	No	Heart disease, diabetes	Management
N/A: not applicable. [#] : see table 1; [†] : addresses depression and anxiety; ⁺ : addresses heart disease, diabetes, anxiety, depression, lung cancer, infections, metabolic syndrome and osteoporosis.					

N/A: not applicable. [#]: see table 1; [†]: addresses depression and anxiety; ⁺: addresses heart disease, diabetes, anxiety, depression, lung cancer, infections, metabolic syndrome and osteoporosis.

A qualitative assessment of what is stated regarding the comorbidities shows that most guidelines mention comorbidity but provide no information as to mechanisms for a relationship with COPD, or how it could affect the assessment, therapy and prognosis of the COPD patient. The exception is the GOLD guideline (guideline 8), in which these aspects are addressed. In addition, the ATS/ERS guideline on rehabilitation partly addresses these topics when considering depression and anxiety.

Discussion

This chapter shows that the guidelines differ overtly with respect to how they address comorbidities in COPD. This relates to the number of times the topic was mentioned, in what aspects of COPD management comorbidity were considered, what type of comorbidities were addressed and, finally, what was actually stated about the various comorbidities.

There was no time trend in the quantitative and qualitative content of comorbidities in the guidelines included in this chapter. The two guidelines with the highest coverage of comorbidities were the oldest and second most recently published (table 2).

This chapter pursued a systematic and predefined strategy for selecting and assessing guidelines to be reviewed. A limitation of the review was the restriction to guidelines written in English. This implies that only the international as well as the US and British guidelines have been evaluated. Other national guidelines were left out, and they represent by far the largest proportion of COPD guidelines. To what extent the English language COPD guidelines are representative of most national guidelines is not known. National guidelines might be influenced by local traditions and reflect the handling of COPD patients better than international guidelines. Conversely, this may also apply to the management of the COPD disease itself and, to a lesser extent, the reference of comorbidities. Many countries have also issued national guidelines that are based on the international recommendations. This may indicate that the findings of this chapter are representative of how most currently applied guidelines present comorbidities in COPD.

One might argue that some of the guidelines reviewed in this chapter were never meant to focus on comorbidities, such as those restricted to specific topics of COPD management, *i.e.* rehabilitation, home treatment of exacerbations and noninvasive ventilator support in respiratory failure. Others were not issued as guidelines but rather position papers within the field of COPD. However, it is important to assess comorbidities like depression, muscle weakness and osteoporosis when planning rehabilitation, while heart disease might be an important cofactor to take into account when treating exacerbations of COPD at home or when assessing the effect of ventilatory support. Hence, although some of the guidelines were restricted to handling specific topics within COPD, one would still expect them to address comorbidities.

The last decade has seen an increased awareness of the importance of comorbidities in patients suffering from COPD [2]. As such, one would expect this to be reflected in an increased focus on this topic in the most recent COPD guidelines. The guideline with by far the most extensive coverage was that of GOLD, which was updated in 2011 (guideline 8). However, the guideline with the second greatest focus on comorbidities was the oldest guideline reviewed in this chapter, covering the last 8 years (guideline 1). The other guidelines had a modest coverage of comorbidities.

Most of the guidelines addressing comorbidities only mentioned the specific conditions without discussing the mechanisms for the various comorbidities in COPD, how they should be assessed or whether some diseases require particular treatment as they occur alongside COPD. An example is the use of β -blockers for treatment of heart disease in COPD patients; it could be worthwhile mentioning that in most COPD cases, β -blockers are safe to use despite the apparent contradiction in treating the patient with both β -agonists and β -blockers.

Despite the fact that the GOLD guideline (guideline 8) addressed comorbidities in various aspects of disease management and had a specific section on comorbidities, there did not seem to be any

consistency in which comorbidities were discussed throughout the manuscript. The GOLD guideline would benefit from one of the authors focusing on comorbidities in all parts of the paper and not only on the section devoted to the topic.

Most patients with COPD have mild or moderate disease and are treated by their general practitioner [14, 15]. In addition, some patients with severe disease have few exacerbations [16] and are rarely or never seen by pulmonologists, but are taken care of by their own doctors [15]. General practitioners obviously have to refer to a variety of different guidelines. Adherence to them will tend to increase if the guidelines are short, uncomplicated and easy to navigate [17, 18]. As such, one could argue that too much focus on comorbidities would work to expand the volume of the guidelines and reduce their implementation. Furthermore, most general practitioners are used to handling, for instance, heart disease, osteoporosis and depression. Hence, it might be enough to mention the comorbidities without any explanations. However, a brief rationale for addressing the various comorbidities in diagnosis, treatment and prognosis of COPD is likely to underline the importance of these conditions to COPD. Addressing comorbidities in the summary of the guidelines will further stress their significance. Only two of the guidelines mentioned comorbidities in the summary (table 2).

There is an increasing appreciation that patients with COPD require an individualised, patient-centred approach that recognises all aspects of the disease, both in terms of assessment and treatment. The management of the disease should be integrated across healthcare sectors and healthcare professionals [13]. Thus, comorbidities are a key issue. This further underlines that comorbidities should receive increased attention in guidelines on COPD.

In conclusion, this brief review has revealed that there are large differences between COPD guidelines as to their coverage of comorbidities. Although there is no trend indicating that recent guidelines focus more on comorbidities than the older guidelines, the increased knowledge of the significance of comorbidities in COPD and the broad coverage of these conditions in the recent GOLD guidelines indicates that future guidelines will focus more on comorbidities in COPD.

Statement of Interest

P.S. Bakke has, within the last 5 years, received lecture fees from GSK, AstraZeneca, Nycomed, Pfizer and Boehringer-Ingelheim, and has received funding for taking part in the ECLIPSE study.

References

1. Thomsen M, Dahl M, Lange P, *et al.* Inflammatory biomarkers and comorbidities in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 982–988.
2. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; 33: 1165–1185.
3. Cazzola M, MacNee W, Martinez FJ, *et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416–469.
4. Bakke PS, Ronmark E, Eagan T, *et al.* Recommendations for epidemiological studies on COPD. *Eur Respir J* 2011; 38: 1261–1277.
5. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
6. Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.
7. British Thoracic Society Guideline Development Group. Intermediate care – hospital-at-home in chronic obstructive pulmonary disease: British Thoracic Society guideline. *Thorax* 2007; 62: 200–210.
8. Qaseem A, Snow V, Shekelle P, *et al.* Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2007; 147: 633–638.
9. Roberts CM, Brown JL, Reinhardt AK, *et al.* Non-invasive ventilation in chronic obstructive pulmonary disease: management of acute type 2 respiratory failure. *Clin Med (Lond)* 2008; 8: 517–521.
10. National Institute for Health and Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. NICE clinical guideline 101. London, Royal College of Physicians, 2010.

11. Qaseem A, Wilt TJ, Weinberger SE, *et al*. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011; 155: 179–191.
12. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of COPD www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf Date last updated: December 2011.
13. Nici L, ZuWallack R, American Thoracic Society Subcommittee on Integrated Care of the CP. An official American Thoracic Society workshop report: the integrated care of the COPD patient. *Proc Am Thorac Soc* 2012; 9: 9–18.
14. Buist AS, McBurnie MA, Vollmer WM, *et al*. International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. *Lancet* 2007; 370: 741–750.
15. Nielsen R, Johannessen A, Benediktsdottir B, *et al*. Present and future costs of COPD in Iceland and Norway: results from the BOLD study. *Eur Respir J* 2009; 34: 850–857.
16. Hurst JR, Vestbo J, Anzueto A, *et al*. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.
17. Boulet LP, FitzGerald JM, Levy ML, *et al*. A guide to the translation of the Global Initiative for Asthma (GINA) strategy into improved care. *Eur Respir J* 2012; 39: 1220–1229.
18. Wood SK, Payne JK. Implementation of National Comprehensive Cancer Network evidence-based guidelines to prevent and treat cancer-related infections. *Clin J Oncol Nurs* 2012; 16: E111–E117.

CME Credit Application Form

(5 CME credits)



This book has been accredited by the European Board for Accreditation in Pneumology (EBAP) for 5 CME credits.

To receive CME credits, read this issue of the Monograph, indicate the correct responses to the educational questions and complete the requested information. To return your application, you can either:

> use this form and return it completed to ERS Publications Office, 442 Glossop Road, Sheffield, S10 2PX, UK; fax to +44-114-2665064; or e-mail to info@ersj.org.uk

> fill in the online form available on the table of contents for the issue at erm.ersjournals.com

Certificates will be e-mailed to the address filled in below. Please allow 4 weeks for processing.

Applicant personal details

ERS Membership No. : Date of Birth (DD/MM/YYYY):
(if known)

Family Name: First Name:

Mailing Address:
.....
.....

Postal Code: City: Country:

Telephone: +..... E-mail:

Educational questions

1. Which one of the following statements is true regarding COPD and its comorbidities?

- ☐ The prevalence of COPD and comorbidities is consistent among different, available epidemiological studies due to a common standard definition and methodology. ☐ Most people with COPD ultimately die of chronic respiratory failure. ☐ Depression is very uncommon in people with COPD. ☐ Inhaled corticosteroids may increase the incidence of pneumonia, yet decrease the incidence of exacerbations.

2. A 60-year-old male presents to your outpatient clinic for evaluation and management of COPD. Which one of the following combinations of comorbidities is the most likely to predict mortality?

- ☐ Coronary artery disease and oesophageal cancer. ☐ Depression and hyperlipidaemia. ☐ Pulmonary hypertension and diabetes. ☐ Stroke and chronic renal failure.

3. Which one of the following statements is true?

- ☐ People with COPD have an increased incidence of lung cancer in excess of their smoking-related risk. ☐ Despite widespread belief, data from the ECLIPSE study did not identify the presence of gastro-oesophageal reflux disease as an independent predictor of frequent COPD exacerbations. ☐ The incidence of osteoporosis in COPD patients is comparable to controls. ☐ AV nodal re-entry tachycardia is the most common arrhythmia in the population with COPD.

Continued on next page

4. Which one of the following statements is false?

☐ In the PLATINO study, the estimated prevalence of COPD in those aged over 40 years was between 8–20%. ☐ The presence of obstruction is supposed to be classified based on the post-bronchodilator lung function. ☐ The definition of COPD is now uniform across GOLD, the ATS and the ERS. ☐ The “fixed ratio” criterion for COPD is simple and accurately estimates COPD prevalence across all age groups.

5. Heart failure can be divided into heart failure with reduced ejection fraction (HF-REF), heart failure with preserved ejection fraction (HF-PEF), and right-sided heart failure (cor pulmonale). How often are these types present in patients with COPD? (Select one of the following.)

☐ HF-REF 20%, HF-PEF 30%, cor pulmonale 50%. ☐ HF-REF 45%, HF-PEF 45%, cor pulmonale 10%.
☐ HF-REF 30%, HF-PEF 50%, cor pulmonale 20%. ☐ HF-REF 49%, HF-PEF 50%, cor pulmonale 1%.

6. Which one of the following diagnostic tests typically has an independent diagnostic value for detecting heart failure in the presence of COPD, and not in those without COPD?

☐ A history of ischaemic disease. ☐ Obesity (BMI >30 kg·m⁻²). ☐ Abnormal apical impulse. ☐ Exclusionary cut-points for natriuretic peptides.

7. Which one of the following statements is true regarding spirometry in patients with heart failure?

☐ Both FEV₁ and FVC can both be decreased by about 20%. ☐ Results are similar in patients with and without signs of fluid retention. ☐ The results with spirometry are not affected by the presence of heart failure. ☐ Diagnosing COPD with spirometry is affected, but not the grading of severity of COPD.

8. Which one of the following statements is true? Drugs for heart failure can be used in patients with COPD:

☐ With the exception of beta-blockers. ☐ With the exception of digoxin. ☐ With no exceptions, when carefully uptitrated and dosed. ☐ With the exception of beta-blockers and digoxin.

9. Which one of the following statements is true? The best way to assess malnutrition in COPD is by:

☐ Measuring body weight. ☐ Calculating BMI. ☐ Assessing fat-free mass. ☐ Assessing fat mass.

10. Which one of the following is not a risk factor for the development of malnutrition in COPD?

☐ Hypoxia. ☐ Hyperactivity. ☐ Decreased food intake. ☐ Medication use.

11. Based on current knowledge, which one of the following is the best treatment for malnutrition in COPD:

☐ Nutritional supplementation. ☐ Exercise. ☐ A combination of nutritional supplementation and physical exercise. ☐ An increase in general food intake.

12. Malnutrition is detrimental to the prognosis in COPD. In the case of obesity, the effect on prognosis is less consistent. Which one of the following statements is true?

☐ Obesity is beneficial to prognosis in severe COPD. ☐ As in the healthy, obesity is detrimental to prognosis. ☐ The long-term effect of obesity in COPD is always beneficial.

13. Which of the following statements is true regarding the epidemiology of overlap syndrome?

☐ The prevalence of overlap syndrome is approximately 17% according to the National Health and Nutrition Examination Survey (NHANES III). ☐ The prevalence of OSAS is as common as 24% in males and 9% in females according to the Wisconsin cohort study. ☐ The prevalence of overlap syndrome is about 1% of the general adult population. ☐ The Wisconsin cohort study found that an AHI of ≥5 events per hour was three times more likely in never-smokers than current smokers.

14. Which one of the following is not a protective factor against OSAS in COPD?

- ☐ Low BMI.
- ☐ Reduced diaphragmatic efficiency due to lung hyperinflation.
- ☐ Diminished REM sleep.
- ☐ Medication: theophylline.

15. Which of the following responses is not a result of intermittent hypoxia associated with OSAS in contributing to cardiovascular diseases?

- ☐ Increased sympathetic nervous system.
- ☐ Systemic inflammation and oxidative stress.
- ☐ Downregulation of the transcription factor NF- κ B pathway.
- ☐ Insulin dysregulation.

16. With regard to overlap syndrome, which one of the following statements is false?

- ☐ Daytime hypercapnia and nocturnal hypoxaemia lead to pulmonary hypertension.
- ☐ The severity of obstructive ventilatory impairment was inversely correlated with the severity of sleep disordered breathing.
- ☐ The inspiratory capacity to total lung capacity ratio correlates with sleep efficiency.
- ☐ Treatment with nasal CPAP can reduce the CT 90.

17. Which one of the following statements is true?

- ☐ COPD can increase depressive symptoms.
- ☐ COPD can increase anxiety.
- ☐ COPD can severely negatively affect the quality of life.
- ☐ All of the above.

18. Which one of the following statements is true? A high score on a mental health screening scale:

- ☐ Is diagnostic of a mental disorder.
- ☐ Should be ignored because of somatic overlap with ageing and COPD.
- ☐ Should be investigated by a clinician with mental health expertise and treated if appropriate.
- ☐ Is likely to be a false positive.

19. Which one of the following statements is false?

- ☐ Depression and anxiety are risk factors for initiating tobacco smoking.
- ☐ Smoking rates amongst those with severe mental illnesses are high.
- ☐ Failure of a tobacco-cessation attempt is not linked to having depressive symptoms.
- ☐ Smoking cessation itself may induce depressive symptoms in individuals with a history of depression.

20. When treating patients with COPD who also have depression, which one of the following statements is true?

- ☐ Cognitive behaviour therapy is indicated for those with severe depression.
- ☐ The safest and most effective pharmacotherapy is amitriptyline.
- ☐ There is level I evidence from COPD populations supporting the use of monoamine oxidase inhibitors.
- ☐ Selective serotonin re-uptake inhibitors are the preferred first-line therapies for controlling depression symptoms.

21. When treating patients with COPD who have an anxiety disorder, which one of the following statements is true?

- ☐ Low-intensity cognitive behaviour therapy-based interventions are recommended first-line treatment.
- ☐ Pulmonary rehabilitation has level II evidence for improving control of anxiety symptoms.
- ☐ Benzodiazepines are recommended first-line therapy to control panic disorder in COPD patients.
- ☐ Interpersonal therapy is contraindicated for social anxiety disorders.

22. Which one of the following statements is true?

- ☐ Anxiety symptoms should not influence the course or treatment of COPD.
- ☐ Depression is part of the normal clinical spectrum of COPD and requires no targeted treatment beyond the usual management of COPD.
- ☐ Because anxiety and depression are so common in COPD, cognitive behaviour therapy should be a core component of COPD management.
- ☐ People with COPD who also have clinical depression have worse health-related quality of life and more hospitalisations than those without comorbid depression.

Continued on next page

23. Regarding the treatment of mental health comorbidities in people with COPD, which one of the following statements is true?

☐ Anxiety symptoms are readily controlled by tricyclic antidepressants. ☐ Panic disorder usually responds to cognitive behaviour therapy. ☐ Chronic disease self-management programmes are more effective at reducing anxiety and depression symptoms in comparison with pulmonary rehabilitation. ☐ All patients demonstrating depressive symptoms should be referred to a psychiatrist or psychoanalyst.

24. How can skeletal muscle strength be best assessed in clinical practice? (Select one of the following.)

☐ It requires high-tech equipment and can hardly be performed in clinical practice. ☐ With a strain gauge and a maximal voluntary contraction. ☐ Using a magnetic or electrical twitch measurement as this avoids motivational bias which would otherwise make results unreliable. ☐ Ask the patient to perform a contraction against manual resistance, scored from 0 (no contraction) to 5 (normal contraction).

25. Which one of the following anabolic drugs could selected patients be currently advised to take to increase skeletal muscle strength?

☐ Testosterone. ☐ Erythropoietin. ☐ Myostatin inhibitors. ☐ Corticosteroids.

26. What is the best way to improve skeletal muscle function in a patient with COPD who is suffering from muscle weakness? (Select one of the following.)

☐ Optimal bronchodilator therapy and inhaled corticosteroids in case of exacerbations. ☐ Adherence to 30 min of physical activity (e.g. walking) per day on most days of the week. ☐ Pulmonary rehabilitation for at least 8 weeks. ☐ Nutritional therapy, including increased protein consumption.

Other titles in the series

ERM 58 – Tuberculosis

Christoph Lange and Giovanni Battista Migliori

ERM 57 – Pulmonary Hypertension

M.M. Hoepfer and M. Humbert

ERM 56 – Paediatric Asthma

K-H. Carlsen and J. Gerritsen

ERM 55 – New Developments in Mechanical Ventilation

M. Ferrer and P. Pelosi

ERM 54 – Orphan Lung Diseases

J-F. Cordier

ERM 53 – Nosocomial and Ventilator-Associated Pneumonia

A. Torres and S. Ewig

ERM 52 – Bronchiectasis

R.A. Floto and C.S. Haworth

ERM 51 – Difficult-to-Treat Severe Asthma

K.F. Chung, E.H. Bel and S.E. Wenzel

ERM 50 – Sleep Apnoea

W.T. McNicholas and M.R. Bonsignore

ERM 49 – Exhaled Biomarkers

I. Horvath and J.C. de Jongste

ERM 48 – Interventional Pulmonology

J. Strausz and C.T. Bolliger

ORDER INFORMATION

Monographs are priced at £45.00/€53.00/US\$80.00 each plus postage.

Postage: Europe: £4.00/€5.00/US\$6.00. Non-Europe: £6.00/€7.00/US\$9.00

For a more detailed postage quote contact the

European Respiratory Society Publications Office directly.

European Respiratory Society Publications Office,

442 Glossop Road, Sheffield, S10 2PX, UK.

Tel: 44 (0)114 267 2860; Fax: 44 (0)114 266 5064; E-mail: sales@ersj.org.uk